An Investigation into Reactivity and Selectivity in Cycloadditions of 1,3-Dipoles with Formamidines.

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This thesis is my own work and has not been submitted for another degree, either at UCC or elsewhere.

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Abstract

The objective of this research was to investigate the synthesis of nitrile oxides and to study their reactivity in 1,3-dipolar cycloadditions with formamidines.

Chapter one looks at the literature surrounding the 1,3-dipolar cycloaddition reaction. It explores the generation of 1,3-dipoles (mainly nitrile oxides) and dipolarophiles (predominantly amidines). It discusses the potential synthetic uses of the 1,3-dipolar cycloadducts. It examines both and inter- and intra-molecular cycloaddition reactions. It recognises the use of the 1,3-dipolar cycloadditions as a successful method in building natural products and oxadiazolines. The decomposition of oxadiazolines as a route to nitriles is also outlined in this chapter.

Chapter two discusses the results of this research candidate. The preparation of nitrile oxide precursors - hydroximoyl halides - is outlined at first. The generation of nitrile oxides is then demonstrated, followed by the preparation of furoxans. Methods for preparing the reference materials (nitriles and ureas), which result from decomposition of oxadiazolines, then follow. The preparation of series of Δ^2-1,2,4-oxadiazolines *via* the 1,3-dipolar cycloaddition reaction is illustrated in this chapter. The selectivity of the addition of nitrile oxides to dipolarophiles was tested by competition reactions, which are also described in this chapter. NMR techniques were used in the study of the kinetics of the 1,3-dipolar cycloadditions used for the preparation of a series of Δ^2-1,2,4-oxadiazolines, which is addressed in this chapter.

Chapter three charts the experimental procedures followed to gain results which are discussed in chapter two. It also outlines all analytical data produced during the course of this research.

Acknowledgements

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we’re still friends! To those that followed and became firm friends- Liam, Colm and Denis L. Moving to the ground floor and sharing with Mike, Charlotte and Kieran - it wasn’t easy, but somehow we didn’t kill each other! Returning to the fourth floor and sharing with Elaine, Hannah and Harry. To great friends I’ve gathered along the way; MT, Ali, Michelle T, Carla, Brian and Norma and those on the UCC ladies soccer team whom I had the privilege to play with.

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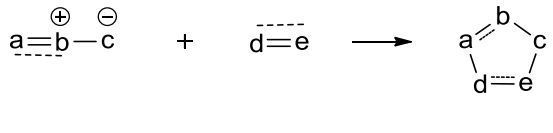
Chapter 1
Introduction

1 1,3-Dipolar cycloadditions

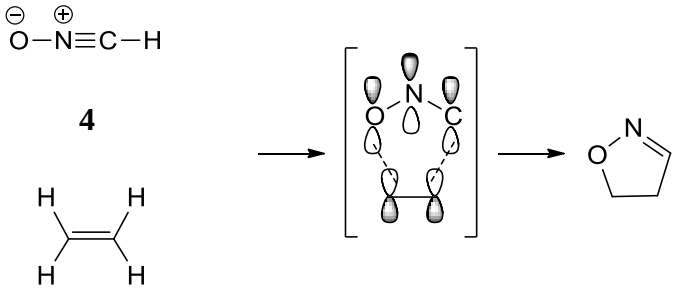
Houk *et al.* described the 1,3-dipolar cycloaddition reaction as a concept, '*in which a formally zwitterionic molecule (the dipole)* **1**, *undergoes 1,3-addition to an alkene or an alkyne, (the dipolarophile)* **2**, *to form a five-membered ring heterocycle* **3**' (Scheme 1).[1] The reaction has been developed into a useful method for five-membered heterocycle synthesis since many 1,3-dipolar species are readily available and are reactive towards a wide range of dipolarophiles.



1 **2** **3**

Scheme 1: 1,3-dipolar cycloaddition[1]

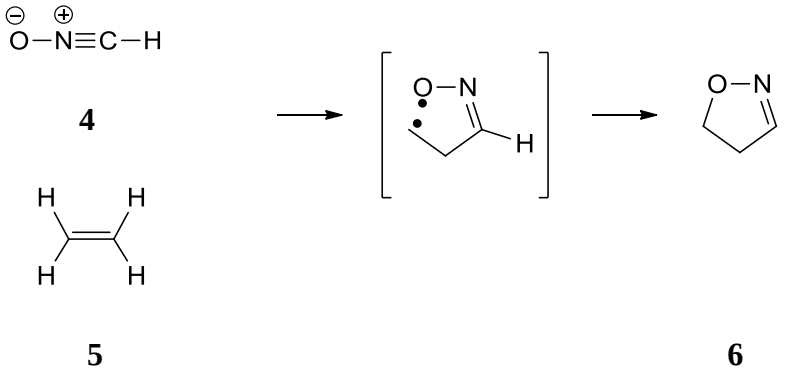
In the 1960s, a well-documented discussion arose regarding the actual mechanism of the 1,3-dipolar cycloaddition reaction.[2] Huisgen favoured a concerted mechanism, whereas Firestone and coworkers proposed a stepwise mechanism. Huisgen's model involved a transition state where the 4π-electron system of the 1,3-dipole (e.g. a nitrile oxide) interacts with the π–bond of the dipolarophile in a concerted pericyclic transition state (Scheme 2).



4 **5** **6**

Scheme 2: Huisgens's mechanistic model

Firestone on the other hand proposed that the reaction proceeds *via* a singlet diradical intermediate (Scheme 3).



Scheme 3: Firestone's mechanistic model

On the basis of the stereoselectivity of the 1,3-dipolar cycloaddition reaction, the dispute was settled in favour of the concerted mechanism. Therefore, Huisgen's model is now generally accepted and the transition state can be analysed using the Fukui frontier molecular orbital approach.[3]

1.1 Orbital interactions

The transition states of the concerted 1,3-dipolar cycloaddition reactions of nitrile oxides are controlled by the frontier molecular orbitals of the substrates,[2h] and the regioselectivity of 1,3-dipolar cycloadditions can be rationalised by frontier orbital theory.[3] Sustmann has classified 1,3-dipolar cycloadditions into three types, designated Types I-III, depending on the nature of the substituents on the dipole and dipolarophile.[4] In Type I, the LUMO of the dipolarophile can interact with the HOMO of the dipole (common for electron-deficient dipolarophiles). In Type III, the HOMO of the dipolarophile can interact with the LUMO of the dipole (common for electron-rich dipolarophiles), and in Type II the frontier orbital energies of the dipole and dipolarophile are very similar and a combination of both modes of interaction can occur (

Figure 1).

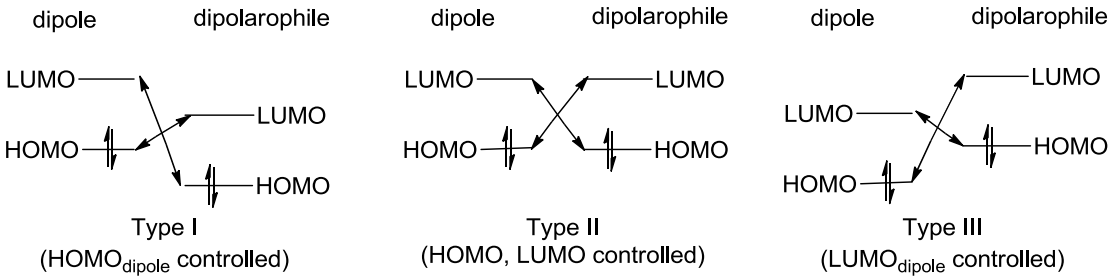


Figure 1: Sustmann's classification of 1,3-dipolar cycloadditions

The allyl anion is a good model for the orbitals of the nitrile oxide as the 1,3-dipole is basically a system of three atoms amongst which are distributed four π-electrons. The predominant orbital interaction in the 1,3-dipolar cycloaddition reaction is that of the $HOMO_{dipole}$ and $LUMO_{dipolarophile}$ (Figure 2).

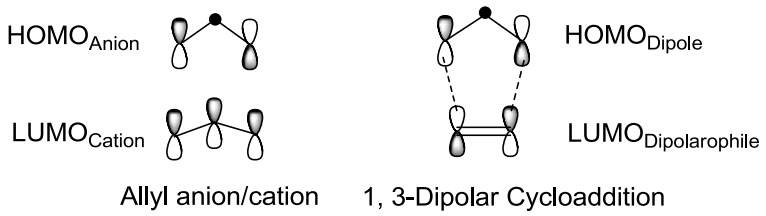


Figure 2: Predominant molecular orbital interaction in the 1,3-dipolar cycloaddition

Once the dominant frontier molecular orbital interaction has been identified, the most favourable direction of combination is that in which the terminal atoms of each component with the largest orbital coefficients interact. This is illustrated in Figure 3 in which state **A** is more stable than state **B**.

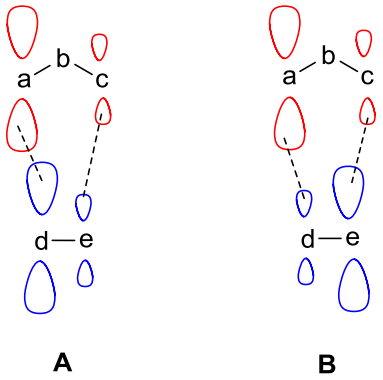
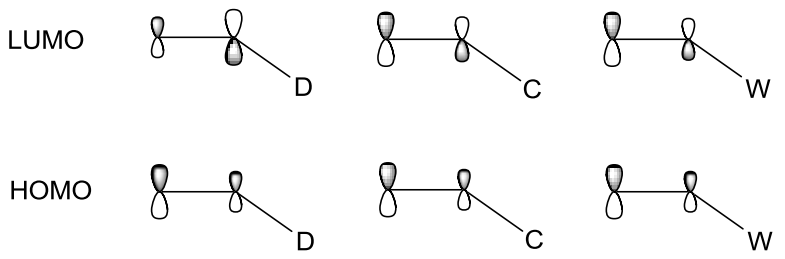


Figure 3: Schematic representation of greater stabilisation of transition state A than B due to different coefficient magnitudes

The frontier orbital coefficients for a large number of dipolarophiles and dipoles have been calculated, and these can be used to rationalise the observed regioselectivities of a range of 1,3-dipolar cycloadditions.[3,5] The effects of the substituents on the magnitudes of coefficients of the frontier orbitals of dipolarophiles have been derived by Houk, and are depicted in Figure 4.[5]



D = electron donating groups, C = conjugated groups, W = electron withdrawing groups

Figure 4: Schematic representation of the effects of the substituents on the magnitudes of coefficients of the frontier orbitals of dipolarophiles as derived by Houk[5]

Controlling stereoselectivity is an important factor in synthesising novel compounds and in developing new synthetic routes to biologically active compounds. The 1,3-dipolar cycloaddition reaction is a very useful reaction from this perspective.

2 1,3-Dipoles

A 1,3-dipole is a structure with 4π electrons bearing a formal positive and a formal negative charge on adjacent atoms. The history of 1,3-dipoles stretches as far back as 1883, when Curtius reported the discovery of diazoacetic ester.[6] His colleague Buchner[7] was the first to describe a 1,3-dipolar cycloaddition reaction in relation to the reaction of a diazoacetic ester with α, β-unsaturated esters. Since then, a variety of 1,3-dipoles have been discovered and classified by Huisgen.[8]

1,3-Dipoles vary greatly in stability. Some can be isolated and stored, and are relatively stable, others are reactive molecules which are generated and reacted *in situ*. 1,3-Dipoles can be classified into two types; the allyl anion type (so-called because it is isoelectronic with the allyl anion) and the propargyl anion type. The allyl anion type is characterised by four electrons in three parallel pz orbitals perpendicular to the plane of the dipole. 1,3-Dipoles of the allyl type are bent, while the presence of a double bond orthogonal to the delocalized π-system in the propargyl anion type gives linearity to the dipole (Figure 5). Examples of the propargyl type 1,3-dipoles are given in Table 1.

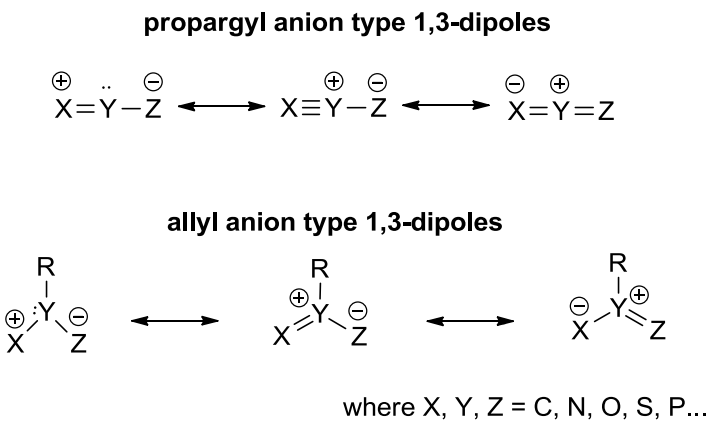
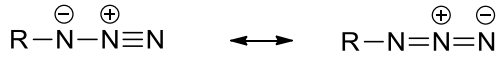
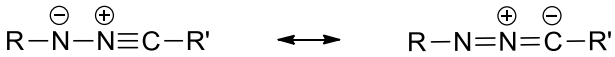
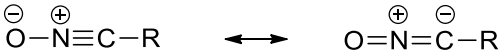
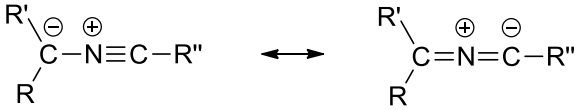
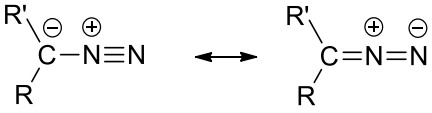


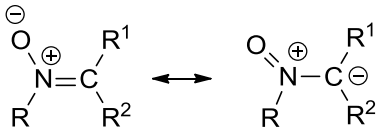
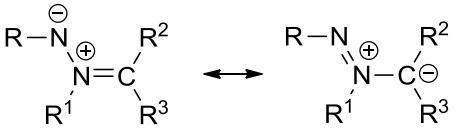
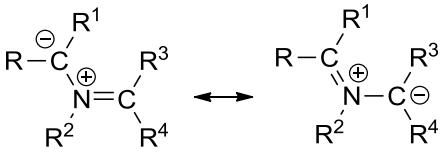
Figure 5: Resonance structures of the propargyl and allyl anion type 1,3-dipoles

Table 1: Examples of linear propargyl anion type 1,3-dipoles

Type	Dipole Structure
Azide	 Stable if aromatic, alkyl azides can be explosive
Nitrile Imine	 Generated and used *in situ*
Nitrile Oxide	 Generated and used *in situ*
Nitrile Ylide	 Generated and used *in situ*
Diazoalkane	 Relatively stable. Diazomethane (R=R´=H) can be stored as a dilute ethereal solution in a freezer for several months.

Examples of 1,3-Dipoles of the allyl type which are bent are shown in Table 2.

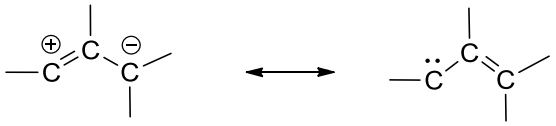
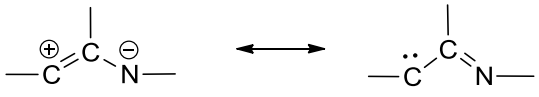
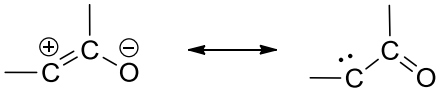
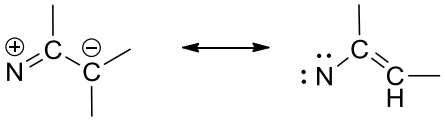
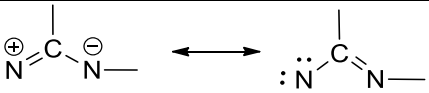
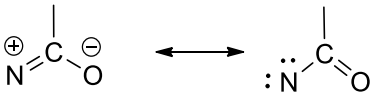
Table 2: Examples of the non-linear allyl type 1,3-dipoles

Type	Dipole Structure
Ozone	 Generated and used *in situ* from dioxygen
Nitrones	 Relatively stable, usually made just before use.
Azomethine Imides	 Generated and used *in situ*
Azomethine Ylides	 Generated and used *in situ*

The 1,3-dipole can be represented by two octet-structures, in which the positive charge is located on the central atom and the negative charge is distributed over the two terminal atoms, and two sextet-structures, wherein two of the four π-electrons are localised at the central atom. The structures shown in Tables 1 and 2 are octet stabilised 1,3-dipoles. Table 3 gives some examples of non-octet stabilized 1,3-dipoles.

Our research concentrated on the behaviour of nitrile oxides. Hence, a more detailed discussion of their properties and reactions follows.

Table 3: Examples of the non-octet stabilised 1,3-dipoles[9]

Type	Dipole Structure
Vinyl carbenes	 Generated and used *in situ*
Iminocarbenes	 Generated and used *in situ*
Ketocarbenes	 Generated and used *in situ*
Vinyl nitrenes	 Generated and used *in situ*
Iminonitrenes	 Generated and used *in situ*
Ketonitrenes	 Generated and used *in situ*

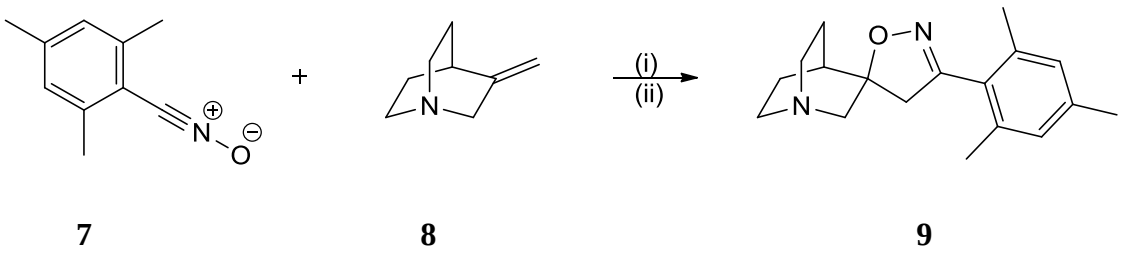
2.1 Nitrile oxides

Nitrile oxides, RCNO, are organic compounds which contain the monovalent functional group –CNO bound directly to another atom, which is usually carbon.[10] They are derivatives of fulminic acid (R = H), the parent nitrile oxide originally described by Ley in 1899.[11] Nitrile oxides are reactive species and are typically generated *in situ* as they are prone to dimerisation. [2i,12] Nitrile oxides are regarded as the 1,3-dipole which has been most frequently and widely utilised in synthetic organic chemistry.[13]

2.1.1 Synthetic uses of nitrile oxides

Mesitonitrile-*N*-oxide **7** is well-documented in the literature.[12d,12i,14] Most interested parties regard it to be a '*stable*' nitrile oxide and it is widely used because it is less prone to dimerisation.[12a,15] Its stability makes it more useful with dipolarophiles which '*may not produce very fast 1,3-dipolar cycloadditions*'. Lee *et al.* noted this in the exploration of the

cycloadditions of nitrile oxides with 3-methylenequinuclidine **8** in the synthesis of spiroisoxazolines **9** (Scheme 4).

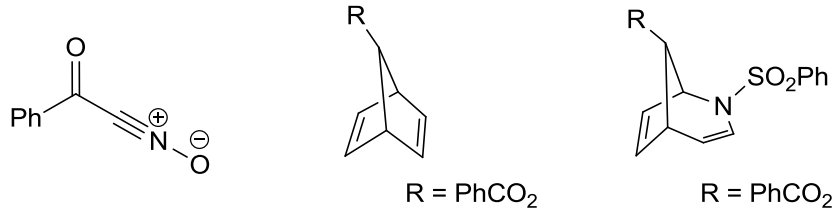


7 **8** **9**

Scheme 4: Reagents: (i) Mesitonitrile-*N*-oxide 7 (0.5 equiv.) at 4°C added over 48 h to 8 (1 equiv.), CH_2Cl_2, 20°C, 24 h; (ii) 7 (0.5 equiv.) at 4°C added over 48 h, 20°C, 24 h. Yield 82%[14a]

The spiro-fused isoxazolidine **9** was viewed as a potential muscarinic agonist for the treatment of Alzheimer's disease.[14a]

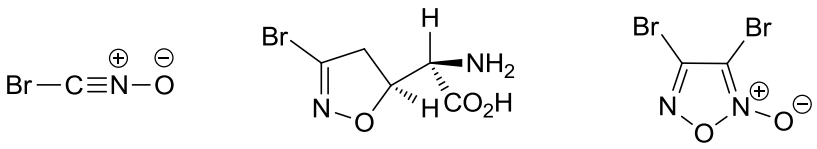
Nitrile oxides have also been examined as tools in the investigation of the stereoselectivity of cycloaddition chemistry. Umano *et al.* found that the cycloaddition of phenylglyoxylonitrile-*N*-oxide **10** to the 7-substituted norbornadiene **11** gave predominantly the *endo*-isomer, but cycloaddition to the 8-substituted 2-azabicyclo [3.2.1] oct-3,6-diene **12** produced the *exo*-isomer (Figure 6).[16]



10 **11** **12**

Figure 6: The structures explored by Umano *et al.*[16]

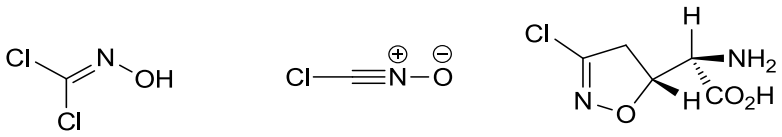
Bromonitrile-*N*-oxide **13** hasbeen used in the direct synthesis of the antitumour agent *erythro*-*α*-amino-3-bromo-4,5-dihydroisoxazole-5-acetic acid **14** which also exhibits anti-bacterial and anti-fungal behaviour (Figure 7). Hagedorn *et al.* noted that dimerisation of **13** was encountered during their investigation, but the furoxan **15** was easily separated from the cycloadduct by extraction with ether.[17]



13 **14** **15**

Figure 7: The products of the reaction of bromonitrile-*N*-oxide 13

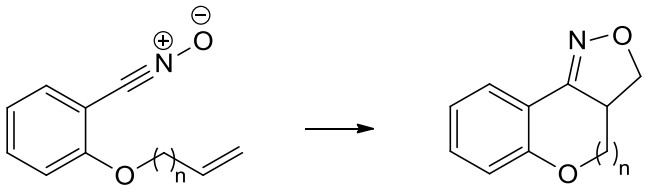
Dichloroformaldoxime **16** has been used as the precursor for chloronitrile-*N*-oxide **17** in the synthesis of acivicin **18** (AT-125) (Figure 8).[17-18]



16 **17** **18**

Figure 8: Dichloroformaldoxime 16, its nitrile oxide 17 and the product 18 of its cycloaddition

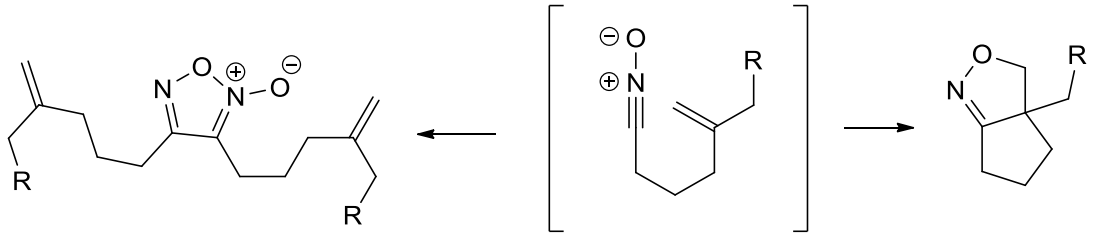
1,3-Dipolar cycloaddition reactions of nitrile oxides with dipolarophiles can take place in both an inter- and intramolecular mode according to Garanti *et al.*, however length of tether between reacting components in the intramolecular cycloadditions has an effect on the rate of cycloaddition (Scheme 5). While investigating the intramolecular cycloaddition, the chain length in **19** varied from n = 1 up to n = 4. Cycloadducts **20** resulting from the cycloaddition were obtained in 47% yield when n = 1 and 17% when n = 2. When the chain length was greater than n = 3, the cycloadduct was not isolated or detected.[19]



19 **20**

Scheme 5: Reagents: i) $NO_{2(g)}$, ether, 0 °C[19]

1,3-Cycloaddition reactions of nitrile oxides with alkenes have been widely reported in the literature. Houk *et al.* explored the reactivity in an intramolecular cycloaddition involving a nitrile oxide to an alkene and found that the nitrile oxide dimerised to **21** rather than forming the heterocycle **22** (Scheme 6).[12j]

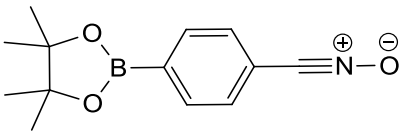


21 **23** **22**

Scheme 6: The reactivity of nitrile oxide 23[12j]

When R was a TMS group, the anticipated cycloadduct was produced. However, in the absence of the TMS group, dimerisation to the furoxan was the principal reaction.

Savage *et al.* explored the versatility of the nitrile oxide containing a pinacolyl boronate ester **24** (Figure 9).[20] This allowed for the synthesis of aryl isoxazolines with the boronate ester function intact and available for subsequent reaction. Arylboronic acids and esters are used in organic synthesis as key intermediates in transition-metal-catalysed carbon-carbon bond forming reactions, e.g. Suzuki reaction.[21]



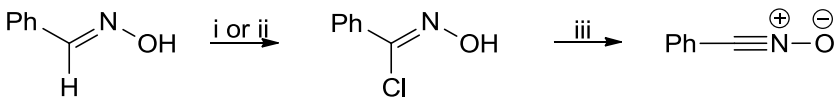
24

Figure 9: The structure of the nitrile oxide 24 investigated by Savage *et al.*

2.1.2 Nitrile oxide synthesis

2.1.2.1 From hydroximoyl chlorides

The procedure for the synthesis (generation) of nitrile oxides was first described by Werner and Buss.[22] This was achieved by chlorination of benzaldoxime **25** to give benzohydroximoyl chloride **26**, followed by dehydrohalogenation with sodium carbonate to generate benzonitrile oxide **27** (Scheme 7). This method is a common route to nitrile oxides *in situ*.



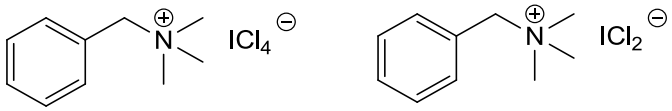
25 **26** **27**

Scheme 7: Reagents: (i) $Cl_{2(g)}$ or (ii) *t*-BuN(CN)Cl, DCM, r.t., <1 min; (iii) NEt_3[22]

Chlorination has been carried out using chlorine, but ring chlorination occurs with aryl systems that are substituted with electron donating groups.[23] There are alternative chlorinating agents, including nitrosyl chloride, *N*-chlorosuccinimide, *t*-butyl hypochlorite, iodobenzene dichloride ($PhICl_2$), chloramine-T (*N*-chloro-*N*-sodio-4-methylbenzenesulfonamide), 1-chlorobenzotriazole, and hydrogen chloride in DMF/ozone.[12c,14d,14g,24] Kaushik *et al.* explored the use of *N*-tert-butyl-*N*-chlorocyanamide as a chlorinating agent in the production of hydroximoyl chlorides.[25]

This novel chlorination method yielded the hydroximoyl chloride of benzaldoxime within a minute of stirring with the reagent in dichloromethane at room temperature. It was reported that the hydroximoyl chloride was isolated in '*virtually quantitative yields*' and with no evidence of over chlorination. The presence of electron donating groups, electron withdrawing groups or an aromatic ring in the oxime molecular structure did not affect the yields/efficiency or the rate of reaction.

Kanemasa *et al.* used benzyltrimethylammonioum tetrachloroiodate **28** as a chlorinating agent and obtained yields of hydroximoyl chlorides in excess of 90% (Figure 10).[26]



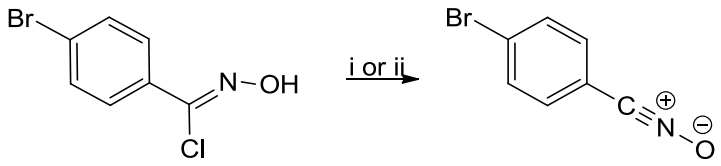
28 **29**

Figure 10: The structure of benzyltrimethylammonium tetrachloroiodate 28 and its salt 29

The salt **28** is a stable yellow solid which makes it easier to dispense accurately. While **28** is not soluble in dichloromethane, the product salt **29** is soluble however, therefore allowing easy identification of reaction completion in that solvent. The salt **29** is poorly soluble in diethyl ether, which facilitates easy isolation of the hydroximoyl chloride '*simply by diluting the reaction mixture with diethyl ether*'.[26] This would only be beneficial when the hydroximoyl chloride is soluble in diethyl ether.

Dehydrohalogenating agents such as amines e.g. triethylamine and tributylamine have been used in place of sodium carbonate.[27] Other alternatives include potassium bicarbonate, aluminium oxide, Florisil®, molecular sieves, hexabutylditin, *bis*-(tributyltin)oxide, tetraphenyltin, tributyltin hydride, silver nitrate and alkali metal fluorides.[18a,24g,27e,28]

Zhu *et al.* investigated the use of two different bases - triethylamine and sodium bicarbonate- on the dehydrohalogenation of the hydroximoyl halide **30** in generating the nitrile oxide **31** (Scheme 8).[29] Sodium bicarbonate decreased the reaction time from 3 days to 1 day as well as increasing the yield of the cycloadduct.



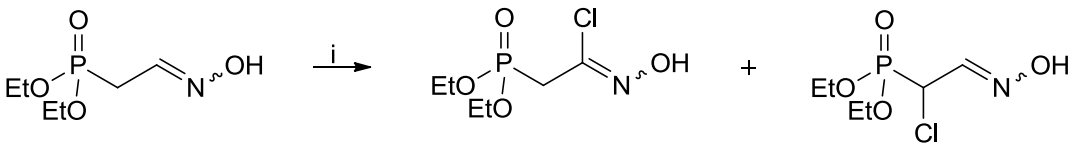
30 **31**

Scheme 8: Reagents: (i) Triethylamine, or (ii) Sodium bicarbonate[29]

Kanemasa *et al.* illustrated the use of organometallics to liberate nitrile oxides from hydroximoyl chloride precursors.[30] Using *n*-BuLi, EtMgBr or Et_2Zn at -30 to -50 ^oC in THF successfully liberated benzonitrile oxide, which was in turn trapped with methyl acrylate in excellent yields (67-91%).

Other variations for nitrile oxide generation include bromination rather than chlorination using *N*-bromosuccinimide, alkali hypobromite, or sodium bromite with a catalytic quantity of tri-*n*-butyltin chloride, and thermal dehydrohalogenation of the hydroximinoyl halide.[12d,24e,31]

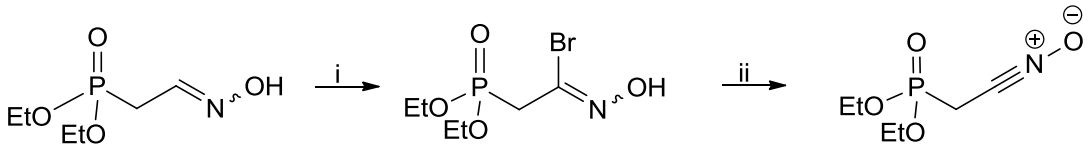
Tsuge *et al.* found that chlorination of the oxime **32** with NCS generated two isomers **33** and **34** (Scheme 9).[32] The yield and isomer ratio of both products from the chlorination reaction could be improved by varying the temperature, the optimum yield achieved was less than 50% (34%).



32 **33** **34**

Scheme 9: Reagents: (i) NCS[32]

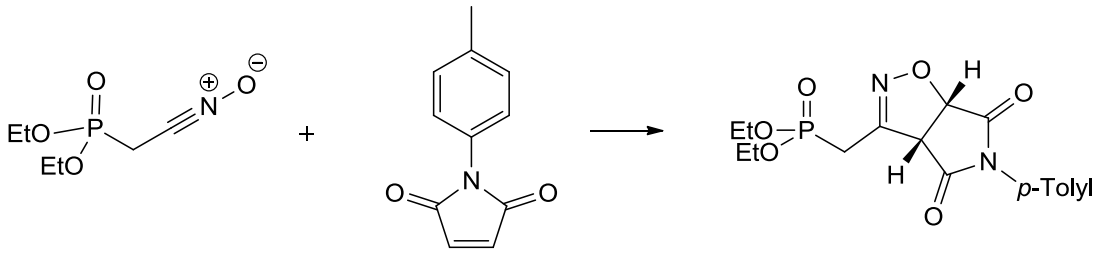
However upon treating **32** with *N*-bromosuccinimide in DMF, whilst the hydroximoyl bromide **35** was not isolated successfully, *in situ* dehydrobromination with triethylamine afforded the nitrile oxide **36** (Scheme 10).



32 **35** **36**

Scheme 10: Reagents: (i) NBS, (ii) NEt_3[32]

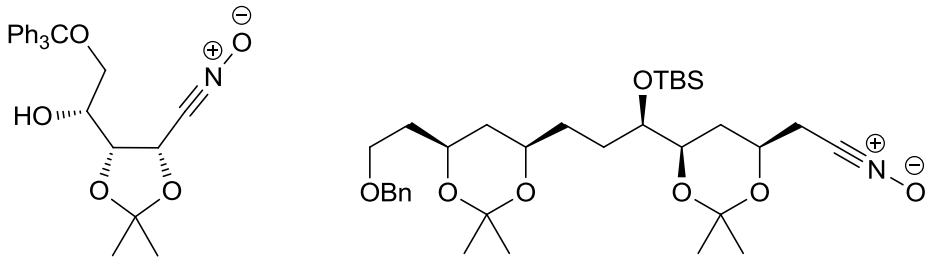
Trapping of the nitrile oxide **36** with *N*-(*p*-tolyl)maleimide **37** the gave the cycloadduct **38** in 80% yield (Scheme 11).



36 **37** **38**

Scheme 11: Nitrile oxide 36 was generated *in situ* and immediately reacted with *N*-(*p*-tolyl)maleimide 37 which gave the cycloadduct 38[32]

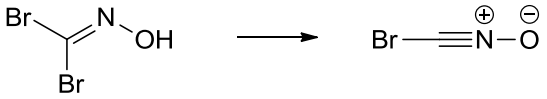
Nitrile oxides have been produced through electrolysis of aldoximes in methanol containing sodium chloride.[33] Examples of nitrile oxides that can be prepared from their aldoximes by this route include the phosphorous-functionalised nitrile oxides, α-(diethylphosphono)-acetonitrile oxide **36**, ribose derivative **39** and the antibiotic precursor **40** (Figure 11).[32,34]



39 **40**

Figure 11: The structures of nitrile oxides 39 and 40 which were prepared from the corresponding aldoximes

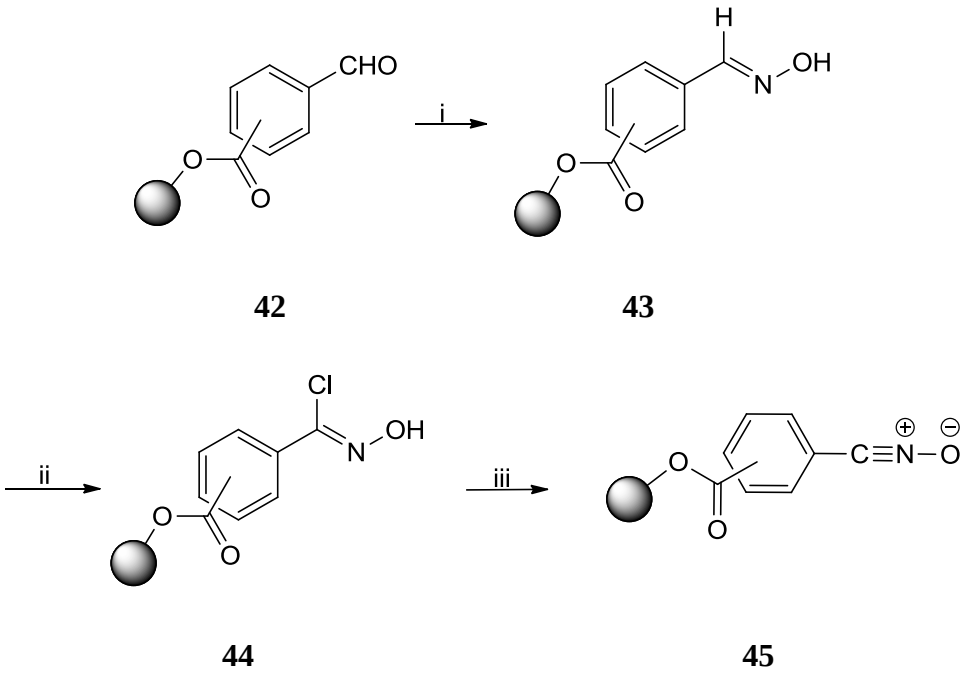
Dibromoformaldoxime **41** gave the nitrile oxide **13** in >95% yield when reacted with potassium carbonate in water (Scheme 12), for direct reaction with water soluble alkenes.[35]



41 **13**

Scheme 12: Conversion of dibromoformaldoxime 41 to its corresponding nitrile oxide 13

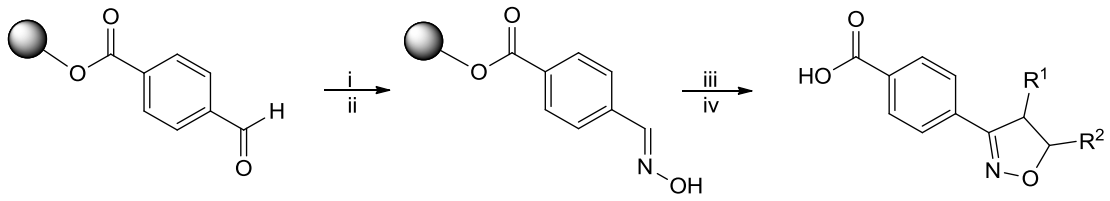
Faita *et al*. investigated solid-supported nitrile oxides as stable and valuable reactive intermediates.[36] Mounting of nitrile oxides onto a solid phase (SP) support facilitated the 1,3-dipolar cycloaddition reactions as the well-known tendency of nitrile oxides to undergo dimerization reactions is reduced under solid-phase (SP) conditions. The cycloadduct could then be easily cleaved from the resin once synthesised. A Wang resin () was employed as the solid state support which was first coupled to *m*- or *p*-carboxybenzaldehyde which gave the resin bound aldehydes **42** (Scheme 13).



Scheme 13: Reagents: (i) $NH_2OH.HCl$, NEt_3, MeOH, r.t., 49 h; (ii) NCS, DCM, r.t., 2 h; (iii) NEt_3, DCM, r.t., 2 h[36]

These aldehydes were then converted into the corresponding aldoximes **43** followed by the hydroximoyl chlorides **44** (Scheme 13). Treatment of **44** with an excess of triethylamine yielded the solid supported nitrile oxides **45**. As the distance between the reactive sites is increased on resins, these nitrile oxides demonstrated added stability. Accordingly, the SP approach might also stabilise other 1,3-dipoles which, under classic solution conditions, must be generated *in situ* and immediately trapped with dipolarophiles. This increased stability will allow easier handling of 1,3-dipoles, which not only simplifies reaction conditions and increases yields, but should also open a route to additional, useful transformations of nitrile oxides that would otherwise be prevented.

Cheng *et al.* explored the potential of supported solid phase nitrile oxides in the synthesis of Δ^2-isoxazolines (Scheme 14) using Wang resin.[37] The reaction of the resin-bound aldehyde **42** with hydroxylamine in the presence of triethylamine in methanol at room temperature affords the desired aldoxime resin **43**. The resin-bound aldoxime obtained was suspended in THF and treated with an excess of commercially available aqueous bleach solution (Clorox®, 10 eq.) to form the nitrile oxide, which reacted *in situ* with alkenes in a one pot synthesis to furnish the corresponding resin-bound Δ^2-isoxazolines. Cleavage of the product from the resin under standard condition (20% TFA in dichloromethane) afforded the desired Δ^2-isoxazolines **46** in good yields (40-94%).

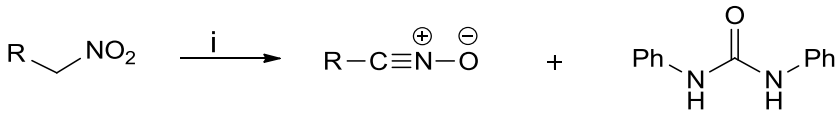


42 **43** **46**

Scheme 14: Reagents: (i) $NH_2OH.HCl$; (ii) NEt_3, MeOH, r.t.; (iii) aq. NaOCl/THF, R^1-CH=CH-R^2; (iv) 20% TFA/ DCM[37]

2.1.2.2 Nitrile oxides *via* dehydration of nitro compounds

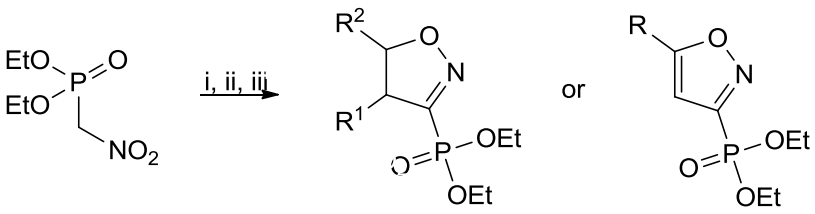
An alternative to the dehydrohalogenation of halooximes as a route to generating nitrile oxides is the dehydration of primary nitroalkanes.[38] This method was highlighted by Mukaiyama in 1960 and has since been referred to as the '*Mukaiyama method*'.[12a,39] The nitroalkanes **47** are dehydrated using phenylisocyanate in the presence of a catalytic amount of triethylamine (Scheme 15). *N*,*N*-Diphenylisourea **48** is the by-product of the reaction of phenylisocyanate with nitroalkanes.



47 **48**

Scheme 15: Reagents: (i) PhNCO, cat. NEt_3, 0 °C-80 °C

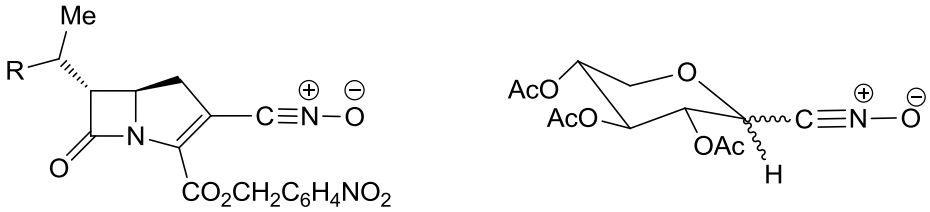
Phosphorus oxychloride, chloroformate esters (e.g. ethylchloroformate), the Burgess reagent, *p*-toluenesulfonic acid and arylsulfonyl chlorides (benzenesulfonyl chloride) have been used as dehydrating agents in the Mukaiyama reaction.[12b,38c,40] Thionyl chloride has also been used as a dehydrating agent with nitroacetamides.[41] One of the advantages outlined by Zhang *et al.*, was that a one-pot reaction could be employed to synthesise 4,5-dihydroisoxazoles and isoxazoles. This process involved the reaction of diethyl nitromethylphosphonate **49** with alkenes or 1-alkynes in the presence of phosphorous oxychloride and triethylamine yielding **50** and **51** respectively (Scheme 16).



49 **50** **51**

Scheme 16: Reagents: (i) $POCl_3$, Et_3N, $CHCl_3$, 0 °C, 20min; (ii) reflux, 2-3 h; (iii) $R^1CH=CHR^2$ or RC≡CH[12b]

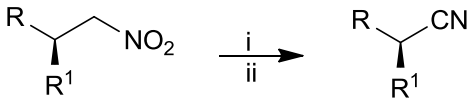
Examples of nitrile oxides produced by this method include the labile carbapenam **52** and xylose **53** derivatives (Figure 12).[42]



52 **53**

Figure 12: The structures of nitrile oxides 52 and 53

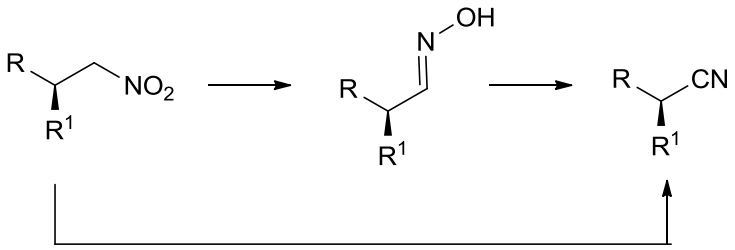
Carreira *et al.* discussed the transformation of optically active nitroalkanes into chiral aldoximes and then into nitriles (Scheme 17).[43] The complete transformation from nitroalkane **54** to nitrile **55** involves the use of relatively inexpensive reagents i.e. potassium hydroxide, benzylbromide.



54 **55**

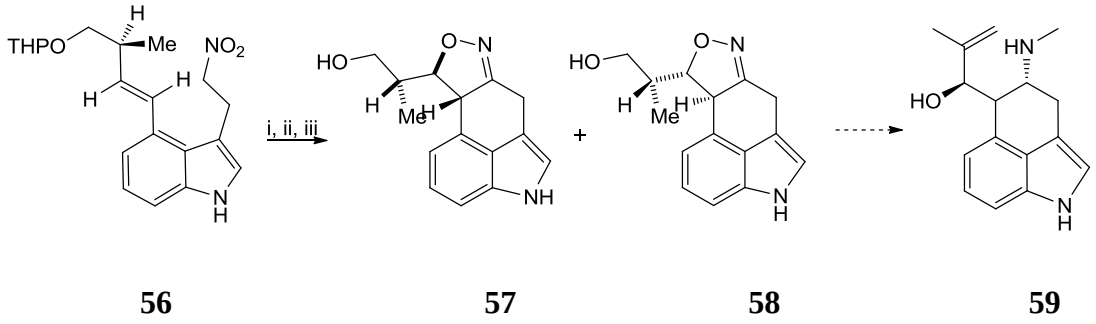
Scheme 17: Reagents: (i) BnBr, KOH, nBu_4NI, THF; (ii) TFAA or $SOCl_2$, NEt_3, THF[43]

The most useful aspect of this synthesis was the formation of the nitrile in good yield (62-73%) without the loss of optical activity. If, however, an optically active nitrile oxide was required, this method also facilitated the synthesis of the optically active aldoxime precursor (Scheme 18).



Scheme 18: Transformation of optically active nitroalkanes into chiral aldoximes and nitriles[43]

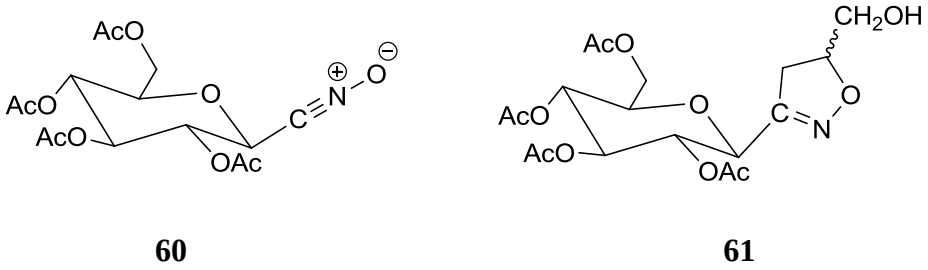
Kozikowski *et al.* used a three step version of this method in converting **56** into the isoxazoline alcohols **57** and **58** in the synthesis of the ergot alkaloid, paliclavine **59** (Scheme 19).[44] Firstly, dipole generation and cycloaddition was achieved by a phenylisocyanate/triethylamine treatment, followed by *N*-acetylation and Dowex W-X8 assisted cleavage of the tetrahydroyranyl (THP) group to yield **57** and **58**.



56 **57** **58** **59**

Scheme 19: Reagents: (i) PhNCO, N Et_3; (ii) Ac_2O, DMAP; (iii) Dowex 50 WX8[44]

Paton *et al.* examined the Mukaiyama method in the generation of glycosyl nitrile oxides such as **60**.[12e] This involved the reduction of primary aliphatic nitro compounds to aldoximes using Sn (II) complexes. The aldoxime was then oxidised with aqueous hypochlorite to the nitrile oxide **60** (Figure 13).

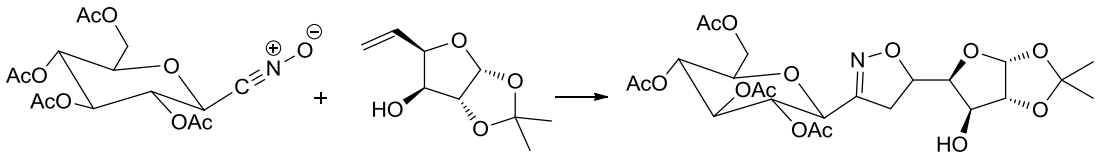


60 **61**

Figure 13: The structures of nitrile oxides 60 and 61

While this Sn(II) reduction method proved useful, it is not infallible as the formation of **61** from allyl alcohol and *C*-disaccharide precursor **63** from D-glucose-derived alkene **62** represent examples of isoxazolines which could not be prepared directly from the nitromethyl

compound by the Mukaiyama method (Scheme 20). Cycloadducts from the derivatives of D-xylose, D-mannose and D-galactose were successfully isolated by Paton *et al*.[12e]

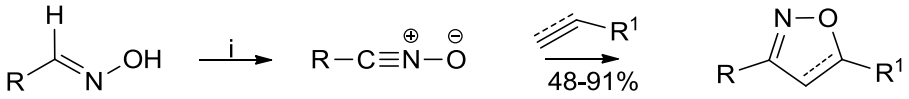


60 **62** **63**

Scheme 20: Reagents: (i) Ether[12e]

2.1.2.3 Nitrile oxides *via* oxidation of oximes

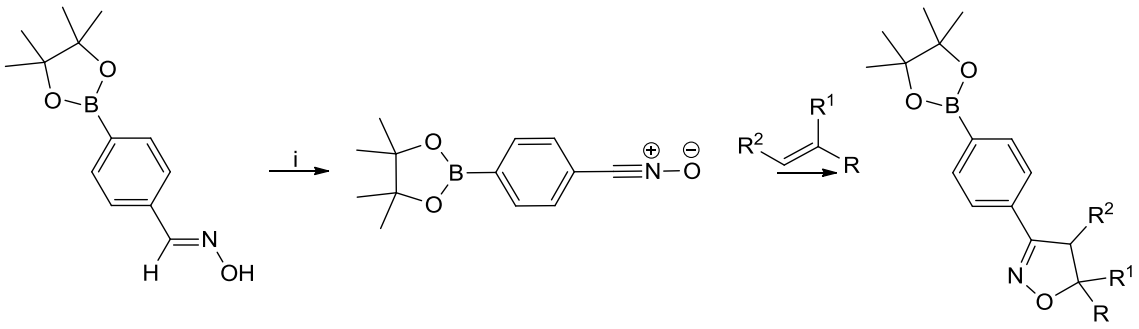
Moriya *et al.* created an oxidizing system using sodium bromite with a catalytic amount of *tri*-butyltin chloride for the preparations of isoxazolines and isoxazoles from aldoximes *via* dipolar cycloadditions (Scheme 21).[31c]



Scheme 21: Reagents: (i) $NaBrO_2$, Bu_3SnCl[31c]

Since sodium bromite had a low reactivity to thedipolarophiles involved, reasonable yields of the cycloadducts could be isolated from a variety of alkenes and alkynes.

Savage *et al.* achieved conversion of oxime **64** into the nitrile oxide **24** using a hypervalent iodine reagent (Scheme 22).[20] The nitrile oxide was trapped *in situ* by alkene dipolarophiles in the synthesis of isoxazolines **65**.

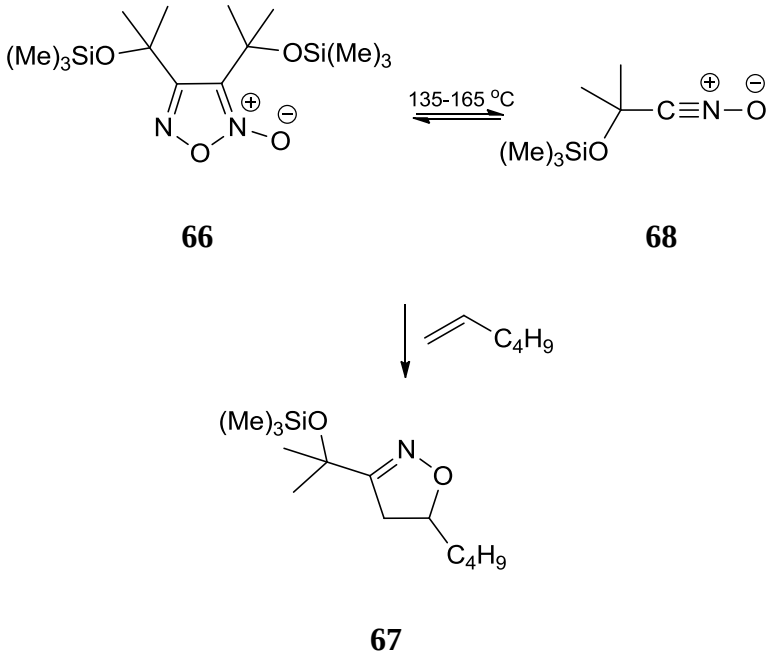


64 **24** **65**

Scheme 22: Reagents: (i) $PhI(OAc)_2$, TFA, Methanol[20]

2.1.2.4 Cycloreversions of furoxans

The cycloreversion of furoxans has also been used to generate nitrile oxides *in situ* under thermal conditions.[12p,45] Curran and Fenk performed the thermolysis of *bis*-[2-[(trimethylsilyl)oxy]prop-2-yl]furoxan (TOP-furoxan) **66** and a clean conversion to the isoxazoline **67** was observed *via* the nitrile oxide **68** (Scheme 23).[46]

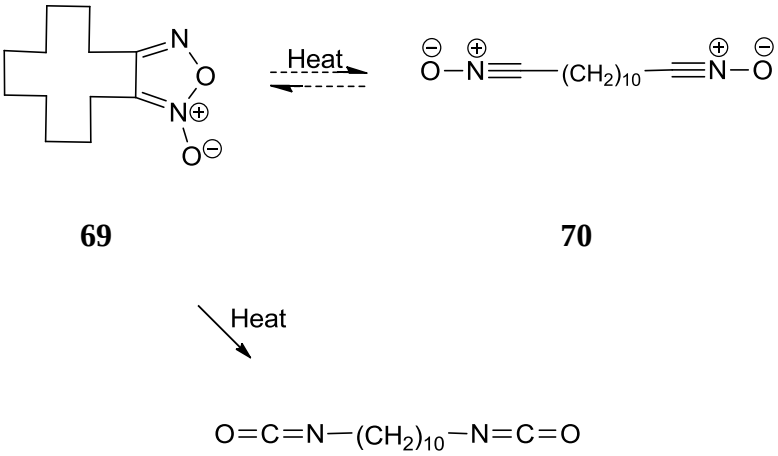


66 **68**

67

Scheme 23: Thermolysis of 66 and conversion to the isoxazoline 67[46]

Crosby *et al*. anticipated that the cycloreversion of furoxan **69** would generate the *bis*-nitrile oxide **70** (Scheme 24).[45a] However, the experimental evidence collected showed that the isocyanate **71** rather than the nitrile oxide **70** was produced when **69** was heated.

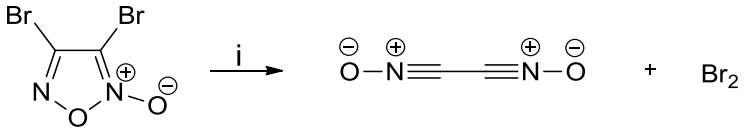


69 **70**

71

Scheme 24: Cycloreversion product of furoxan 69 produced isocyanate 71[45a]

Dibromofuroxan **15** is another furoxan which does not liberate the expected nitrile oxide **13** upon heating (Scheme 25). Westwood *et al.* established that bromine gas was liberated and cyanogen-*bis*-*N*-oxide **72** was formed upon heating **15**.[12o] IR absorptions of 2227 cm^{-1} and 1259 cm^{-1} which were attributed to '*one molecular species*', and assigned to **72**, were observed for the principal reaction product.

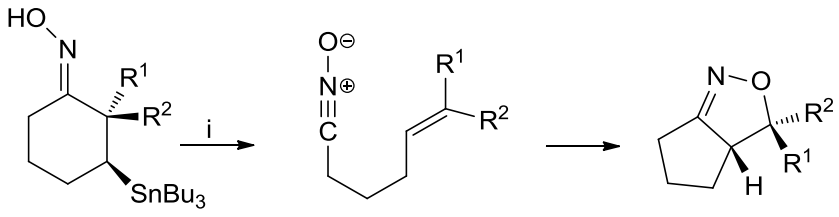


15 **72**

Scheme 25: Reagents: (i) Heat[12o]

2.1.2.5 From stannyl oximes

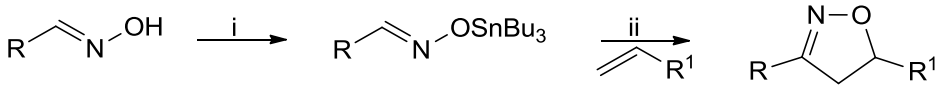
A novel method of nitrile oxide production was devised by Nishiyama *et al.*, whereby oxidative fragmentation of *β*-stannyloximes gave nitrile oxides and alkenes simultaneously, with control of the stereochemistry of the alkenes (Scheme 26).[47]



73 **74** **75**

Scheme 26: Reagents: (i) $Pb(OAc)_4$, $NaHCO_3$[47]

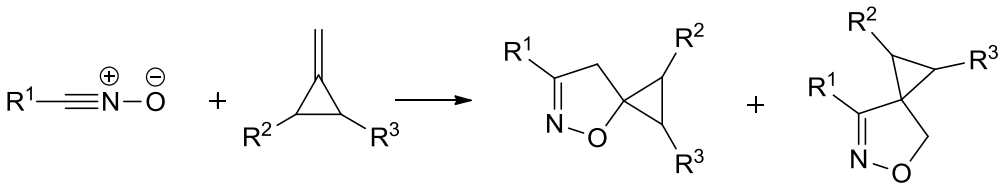
Moriya *et al.* have also explored the production of nitrile oxides from oximes. *O*-Tributylstannyl oxides **76** were treated with alkenes to afford the corresponding isoxazolines **77** in moderate to good yields (Scheme 27).[28g,48]



78 **76** **77**

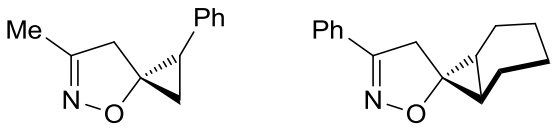
Scheme 27: Reagents: (i) $(Bu_3Sn)_2O$; (ii) *t*-BuOCl[28g,48]

De Sarlo *et al.* explored the 1,3-dipolar cycloaddition reaction of nitrile oxides with methylenecyclopropanes (Scheme 28).[49]



Scheme 28: 1,3-Dipolar cycloaddition reaction of nitrile oxides with methylenecyclopropanes[49]

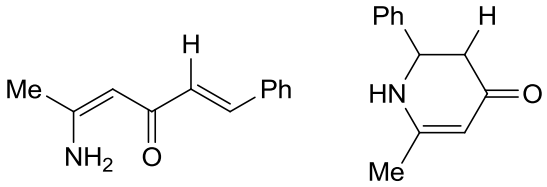
High diastereoselectivity was noted when substituents were present on the cyclopropane ring yielding products such as **79** and **80** (Figure 14). This result was attributed to the '*preferred approach of the dipole from the less hindered face of the dipolarophile'*. The structure **80** was supported by the lack of a nuclear Overhauser effect (nOe) on the protons of the isoxazoline methylene group and suggested this originated from rapid conformational equilibrium of the boat-cyclohexane. This makes sense, because if the structure was the other diastereisomer, then an nOe would have been observed with the cyclopropane protons in a rigid conformation.



79 **80**

Figure 14: Cycloaddition products 79 and 80

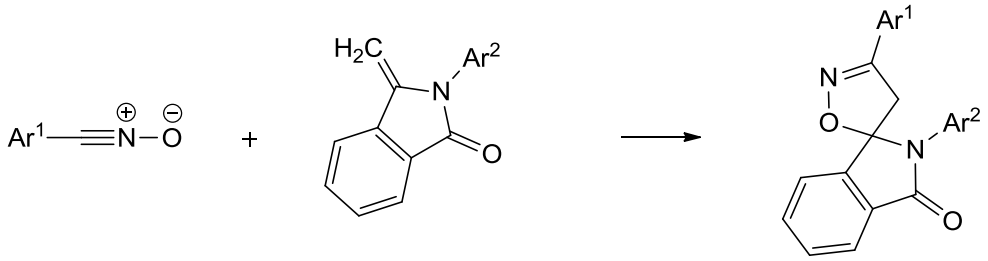
Interestingly, De Sarlo *et al*. also carried out rearrangements of the spiro-fused compounds including **79**, and isolated enaminones **81** and pyridones **82** (Figure 15).[49] In some cases, just heating the heterocycles resulted in the rearrangement.



81 **82**

Figure 15: Isolated products 81 and 82

Other examples of spiroheterocycles resulting from cycloaddition of nitrile oxides to dipolarophiles includes those highlighted by Howe *et al.*.[50] Aromatic nitrile oxides **83** were reacted with *N*-aryl-3-methylenephthalamides **84** to produce spiroheterocycles **85** in good yields (66-78%) (Scheme 29).



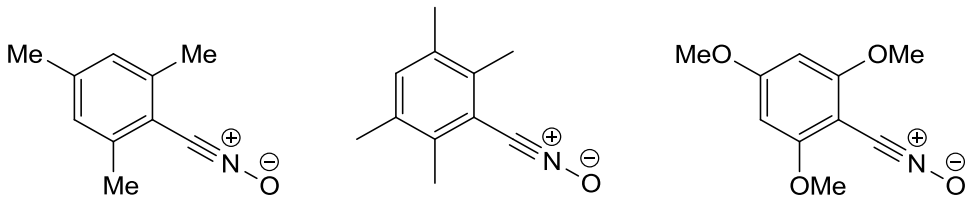
83 **84** **85**

Scheme 29: The formation of spiroheterocycles 85 [50]

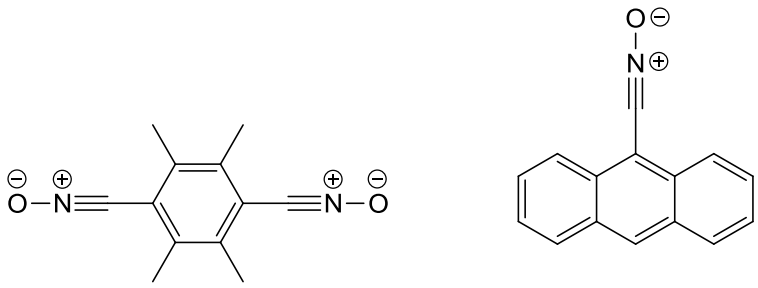
2.1.3 Nitrile oxide stability

Nitrile oxides are known in the literature for being prone to dimerisation.[10,12c,24k,51] Lowe *et al.* explored aromatic nitrile oxides and found that the '*rate of dimerisation depends upon the nature of the the substituent on the aromatic ring*'.[52] It was recognised that the greater the electron donating ability of the substituent on the aromatic ring, the faster the dimerisation. Grundmann *et al.* studied the stability of nitrile oxides in detail.[12d] This work established that aromatic nitrile oxides can be kinetically stabilised with sterically hindered groups.[12d,12r] The focus of the investigation was on aromatic nitrile oxides bearing substituents at the *o,o'*-positions such as methyl, ethyl or methoxyl.

2,4,6-Trimethylbenzonitrile oxide **7**, 2,3,5,6-tetramethylbenzonitrile oxide **86**, 2,4,6-trimethoxybenzonitrile-*N*-oxide **87**, tetramethylterephthalo-*bis*-nitrile oxide **88** and anthracene-9-yl-nitrile oxide **89** were all isolated as '*well-crystallised solids*' (Figure 16).



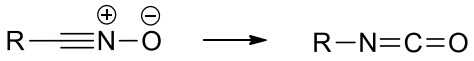
7 **86** **87**



88 **89**

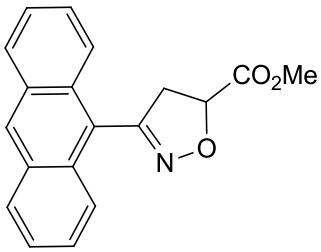
Figure 16: Sterically hindered nitrile oxides

Grundmann *et al.* also tried to force the dimerisation of these nitrile oxides by heating them above their melting points, or by heating them to reflux in high boiling solvents such as xylene. This afforded the corresponding isocyanates rather than the furoxan dimers (Scheme 30).



Scheme 30: The conversion of nitrile oxides to the corresponding isocyanates

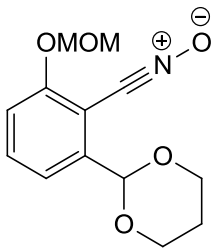
Moriya *et al.* also investigated the reactivity of anthracene-9-yl-nitrile oxide **89** by reacting it with methyl acrylate and isolated the isoxazoline **90** in 68% yield (Figure 17).[31c]



90

Figure 17: The structure of isoxazoline 90

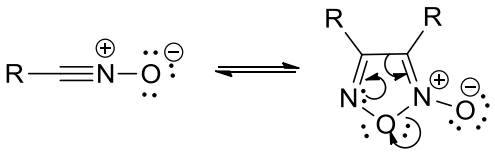
Suzuki *et al.* also explored the use of *o,o*'-disubstituted aromatic nitrile oxide **91** as a potentially '*stable*' structure (Figure 18).[28d] This nitrile oxide provided a synthetic route to highly functionalised isoxazole derivatives in yields up to 85%.



91

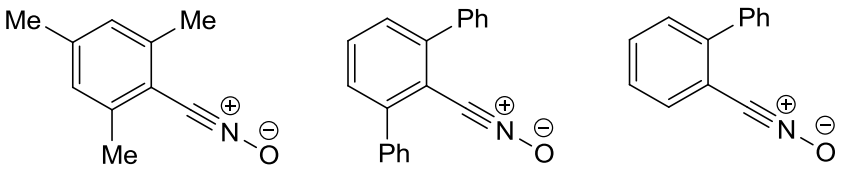
Figure 18: The structure of nitrile oxide 91

As discussed earlier in this chapter (refer to section: 'Nitrile oxides from hydroximoyl chlorides'), Faita *et al*. explored the mounting of nitrile oxides onto a solid phase (SP) support.[36] This work found that the well known tendency of nitrile oxides to undergo dimerisation reactions is reduced under SP conditions (Scheme 31). It was postulated that, the SP approach might also stabilise other 1,3-dipoles which, under classic solution conditions have to be generated *in situ* and immediately trapped by reacting dipolarophiles and found that supported nitrile oxides could in fact be stored in a dry and cool place for at least one day.



Scheme 31: Dimerisation of the nitrile oxide to the furoxan

Preparing more stable nitrile oxides has its benefits also. If dimerisation of the nitrile oxide to the furoxan (Scheme 31) is a problem, then using nitrile oxides that are stable as a result of steric shielding, such as 2,4,6-trimethylbenzonitrile oxide **7**, is attractive.[53] Groundwater *et al.* synthesised a *bis-ortho* substituted nitrile oxide **92** and postulated that the relatively long lifetime of this nitrile oxide **92** could be attributed to resonance stabilisation and steric shielding (Figure 19).[12c] The *ortho*-substituted nitrile oxide **93** also exhibits stability and dimerisation products from these nitrile oxides have yet to be encountered, i.e. they are kinetically stable.

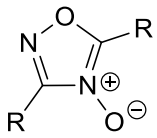


7 **92** **93**

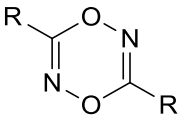
Figure 19: The structures of nitrile oxides 7, 92 and 93

Houk *et al.* outlined the dimerisation of nitrile oxides leading to three potential products (Figure 20).[12h] Firstly, 1,2,5-oxadiazole-2-oxides, more commonly referred to as furoxans, are easily formed. Under acidic or basic conditions, Houk *et al.* observed that nitrile oxides can also dimerise to give either 1,2,4-oxadiazole-4-oxidesor symmetric 1,4-dioxa-2,5-diazines (Figure 20).

1,2,5-oxadiazole-2-oxides



1,2,4-oxadiazole-4-oxides



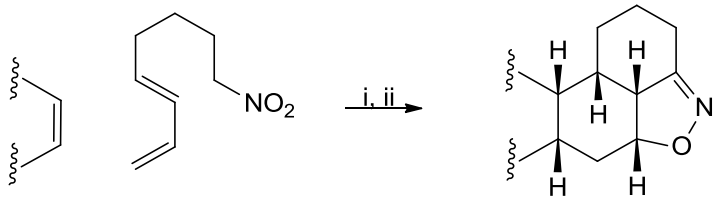
1,4-dioxa-2,5- diazines

Figure 20: Dimerisation products of nitrile oxides

The 1,2,5-oxadiazole-2-oxides structure is the most common product from the dimerisation of nitrile oxides and is well documented in the literature.[12c-e,12h-j,41] Physically adding the hydroximoyl halide precursor in a more dilute solution can retard dimerisation. Alternatively, following Kamimura *et al.*, using a syringe pump to add the solution of the hydroximoyl halide can help to slow down the dimerisation process.[12z] Balsamini *et al.* noted the half-life of *p*-nitrobenzonitrile oxide to be '*about one month at room temperature in diethyl ether*'.[54]

2.1.4 Synthetic uses of 1,3-dipolar cycloadditions

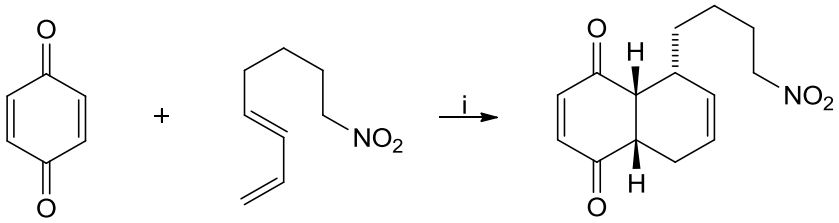
The construction of multiple fused carbocyclic systems as a synthetic route to steroids was investigated by Kozikowski *et al.*.[55] It was envisaged that a [4+2]-cycloaddition process followed directly by a [3+2]-cycloaddition would result in the formation of a tetracyclic structure which would possess five new stereogenic centres (Scheme 32).



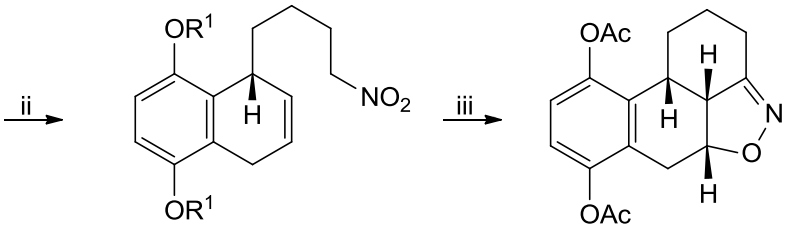
94 **95** **96**

Scheme 32: Reagents: (i) Heat, (ii) PhNCO, NEt_3[55]

The synthetic scheme (Scheme 33) involved intermolecular cycloaddition followed by dipole generation and an intramolecular nitrile oxide cycloaddition which provided the cycloadduct **97** in 83% yield.



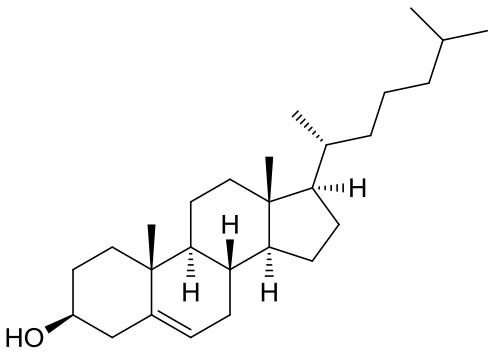
98 **99** **100**



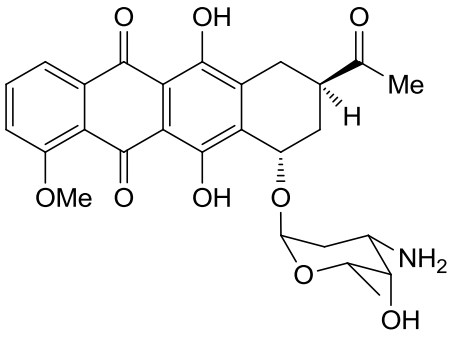
101 **97**

Scheme 33: Reagents: (i) Toluene, 110 ^{o}C, 15 h (100%); (ii) Ac_2O, py (70%); (iii) PhNCO, NEt_3, C_6H_6, 15 h (83%)[55]

This served to demonstrate the potential for building natural products of the steroid (e.g. cholesterol **102**) and anthracycline (e.g. daunomycin **103**) type (Figure 21).



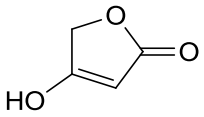
102



103

Figure 21: Natural products cholesterol 102 and daunomycin 103

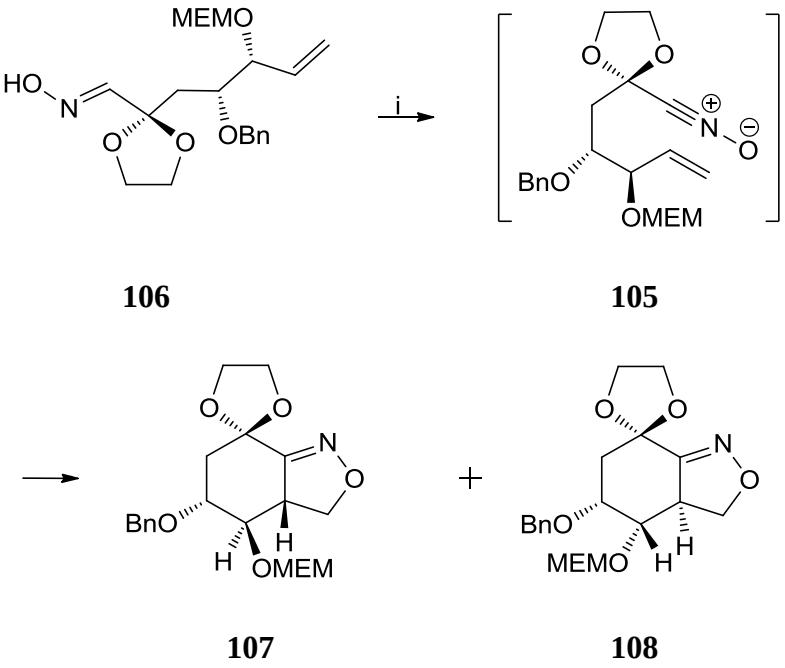
An intramolecular 1,3-dipolar cycloaddition reaction has been utilised as the key reaction in the total synthesis of calicheamicin γ_1-a member of the enediyne class of anti-tumour antibiotics from tetronic acid **104** (Figure 22).[56]



104

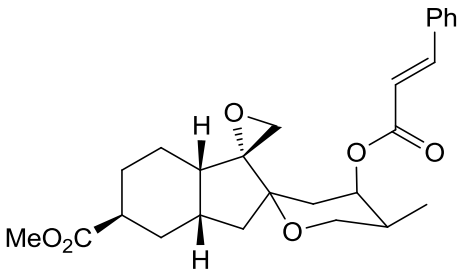
Figure 22: Tetronic acid 104

The cycloaddition reaction of the nitrile oxide **105** derived from **106**, which is a derivative itself of **104**,yields two products **107** and **108** (Scheme 34). Both epimers were isolated in 65% combined yield and in a ratio of 4:1 in favour of **107**.



Scheme 34: Reagents: (i) NaOCl, CH_2Cl_2/H_2O, 0 °C[56]

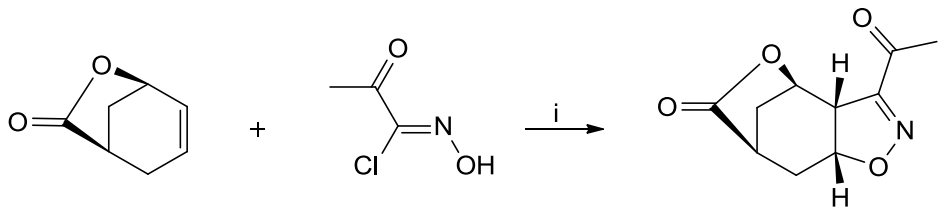
Martin *et al.* explored the application of nitrile oxide cycloadditions in the synthesis of (+)-phyllanthocin **109** (Figure 23).[31e] (+)-Phyllanthocin was intially regarded as a potential anti-cancer agent which was isolated from the ethanol extract of the roots of *Phyllanthus acuminatus.*



109

Figure 23: (+)-Phyllanthocin 109

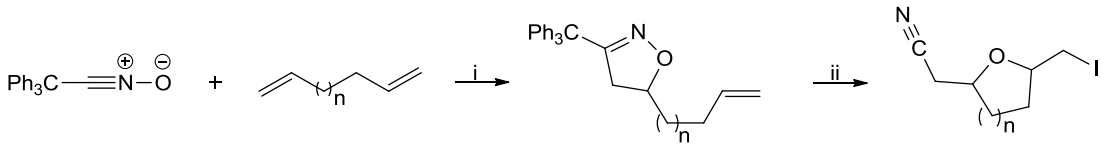
The total synthesis of (+)-phyllanthocin was realised by the recognition of '*the synthetic equivalency of a β–hydroxyketone moiety with an isoxazoline ring*'.[31e] This isoxazoline ring **110** was accessible *via* [3+2] dipolar cycloaddition of a nitrile oxide (thermally generated *in situ*) with an alkene **111** (Scheme 35).



111 **112** **110**

Scheme 35: Reagents: (i) Heating to reflux in toluene[31e]

Kurth *et al.* explored the synthesis of spiroketals, tetrahydrofurans and tetrahydropyrans by way of the products of the cycloaddition of triphenylacetonitrile oxide **113** with *α,ω*-dienes **114** (Scheme 36).[57] It was envisaged that increasing the chain length of the diene (from 7 to 8) would give rise to a tetrahydropyran (from 1,6-heptadiene, n = 2) and an oxepane (from 1,7-octadiene, n = 3).

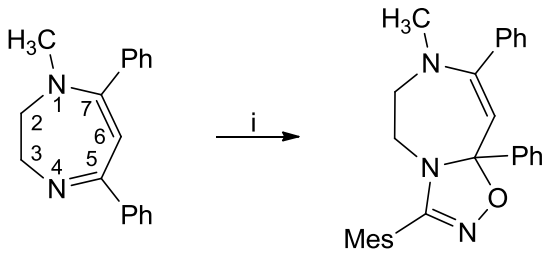


113 **114** **115** **116**

Scheme 36: Reagents: (i) Benzene, 25 °C; (ii) I_2, DCM[57]

More recent work by Kurth *et al.* explored the same chemistry, but had the nitrile oxide moiety resin bound.[38b] Results indicated that carrying out the cycloaddition while the nitrile oxide was tethered to a resin allowed for a smaller excess of dipolarophile to be used (2-3 equivalents *versus* 8 equivalents in the non-resin bound reaction) with a noted increase in yield. It was surmised that the '*reaction most likely to benefit from the polymer-supported protocol is the 1,3-dipolar cycloaddition, in which isoxazoline production by* mono-*addition would be expected to predominate over bis-addition'*.

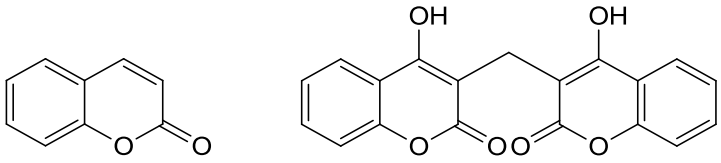
Another interesting result by Baouid *et al.* was the reaction of a 1,4-diazepine **117** with mesitonitrile-*N*-oxide (Scheme 37).[58] While the reaction was slow (7 days), it was completely *peri*- and regioselective. The bicyclic monoadduct **118** which was isolated in 95% yield, showed that the potential dipolarophilic alkene group [C(6)=C(7)] did not react, even when an excess of nitrile oxide was used (2 equiv.).



117 **118**

Scheme 37: Reagents: (i) Mesitonitrile-*N*-oxide, ether, r.t.[58]

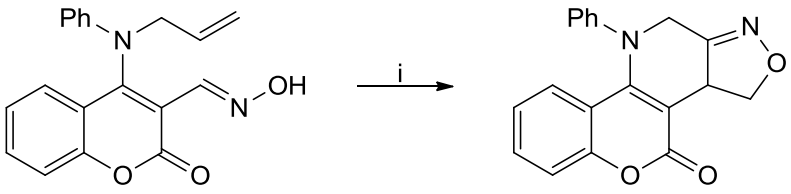
Zecchi *et al.* carried out 1,3-dipolar cycloaddition reactions of nitrile oxides with coumarin **119** as the dipolarophile (Figure 24).[59] It was anticipated that this method could predicate a synthetic route to annulated coumarins, a class of compounds which includes several natural products such as dicoumarol **120**. However, no further developments are evident to date.



119 **120**

Figure 24: Coumarin 119 and dicoumarol 120

More recent investigations by Bhuyan *et al.* within this area explored an intramolecular cycoladdition within the coumarin structure itself (Scheme 38).[60] The 1,3-dipolar cycloaddition reaction was carried out by generating the nitrile oxide from the reaction of **121** with sodium hypochlorite in presence of triethylamine. The *in situ* generation dipole underwent intramolecular cycloaddition to the uncongugated double bond to afford the cycloadduct dihydroisoxazolo[3',4':4,5]pyrido[2,3-*c*]coumarin **122** in 75% yield.

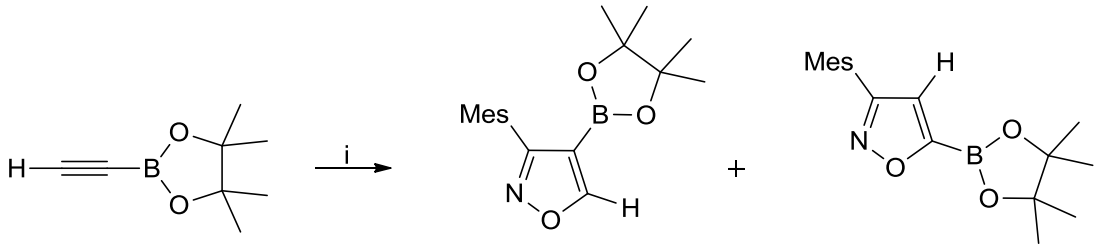


121 **122**

Scheme 38: Reagents: (i) NaOCl, NEt_3, dichloromethane[60]

1,3-Dipolar cycloaddition reactions can provide a diverse range of products as confirmed by Harrity *et al.*.[12i,61] The 1,3-cycloaddition reaction of nitrile oxides with alkynylboronates **123**

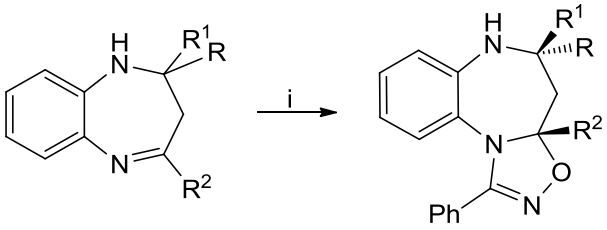
yielded isoxazoleboronic esters **124** and **125** (Scheme 39). The [3+2] cycloaddition reaction offered a relatively simple route to isoxazoleboronic esters in appreciable yield (59%) with good levels of regiocontrol- **124**:**125** (77:23).



123 **124** **125**

Scheme 39: Reagents: (i) Mesitonitrile-*N*-oxide[12i,61]

Investigations into benzodiazepine derivatives with heterocyclic rings annelated at the '*a*' [3-6], '*c*' [7] or '*d*' [8] sides of the heptatomic system have gathered interest. Romeo *et al.* investigated fusing the heterocyclic system to the benzodiazepine ring *via* a 1,3-dipolar cycloaddition with a nitrile oxide to give the cycloadduct.[62] The pharmacological acitivity of the benzodiazopene appears to be enhanced by the addition of a further heterocyclic ring to the benzodiazepine moiety. They successfully extended the 1,3-dipolar cycloaddition strategy to develop a pathway to 1,5-benzodiazepines which incorporated a 1,2,4-oxadiazoline nucleus fused to the '*a*' edge of the heptatomic ring. The reactions themselves proceeded smoothly with the new heterocycles being isolated in good yields (Scheme 40).

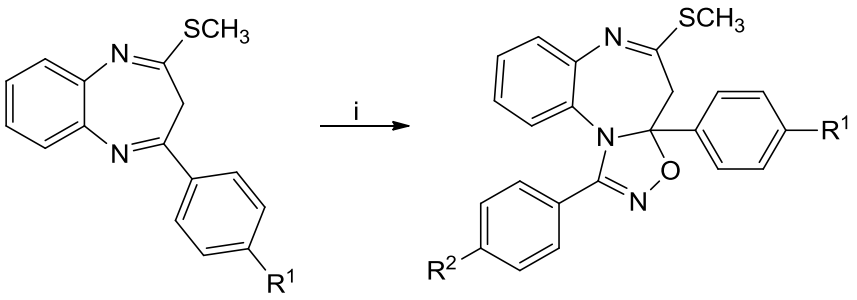


126a R = R^1 = R^2 = Me **127a** R = R^1 = R^2 = Me

126b R = H, R^1 = Ph, R^2 = Me **127b** R = H, R^1 = Ph, R^2 = Me

Scheme 40: Reagents: (i) Benzohydroximoyl chloride, NEt_3[62]

Cortes *et al.* further investigated this reaction by fusing the benzodiazepine ring **128** *via* a 1,3-dipolar cycloaddition to a nitrile oxide to give the cycloadduct **129** (Scheme 41).[63]

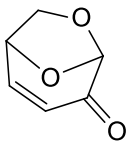


128 **129**

Scheme 41: Reagents: (i) $R^2C_6H_4CNO$[63]

3 Dipolarophiles

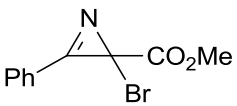
The most common dipolarophiles tend to be alkenesor alkynes, but may also be nitriles, imines, thiocarbonylsand acrylamides.[12a,14a,64] [27b,65] Paton *et al.* investigated the use of levoglucosenone **130** - a cellulose derived *α,β*–unsaturated bicyclic ketone-as a dipolarophile in 1,3-dipolar cycoaddition reaction with benzonitrile oxide (Figure 25).[51a]



130

Figure 25: Levoglucosenone 130 as a dipolarophile

The reactivity of dipolarophiles varies greatly. Imines have exhibited a low reactivity to 1,3-dipoles. Pinho e Melo *et al.* explored the use of 2H-azirine ring systems **131** as a more reactive imine type dipolarophile in 1,3-dipolar cycloadditions (Figure 26).[65e] It was hypothesised that the inherent strain in the ring system would make **131** much more reactive than corresponding alkylimines. Cycloadditions were attempted with diazomethane, however, only complex mixtures of compounds were obtained.



131

Figure 26: 2H-Azirine ring system used as a dipolarophile

In summary, the simplicity and efficacy of the 1,3-dipolar cycloaddition reaction allows it to be embraced in modern synthetic methods and technologies. It has been explored by Gallardo *et al.* in the generation of liquid crystals with success.[66] Its scope can accommodate a wide variety of conditions such as ionic solvents.[12t] In some cases, the 1,3-dipolar cycloadditions are reversible by thermolysis.[67]

3.1 Amidines

Amidines are structures in which an amine group is attached to the carbon atom of an imine (Figure 27). Amidines have been well documented in the literature.[68]

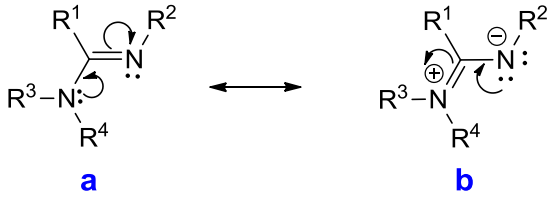
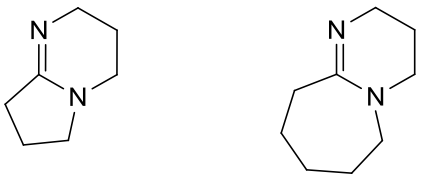


Figure 27: Resonance forms of amidines

Amidines are stronger bases than amides or amines and are among the strongest neutral bases.[69] Two frequently used amidine bases are 1,5-*di*aza*bi*cyclo[3.4.0]nonene-5 (DBN, **132**) and 1,8-diazabicyclo[5.4.0]undecene-7 (DBU, **133**) (Figure 28). These are '*easier to make, more stable, and less volatile than simpler amidines*'.



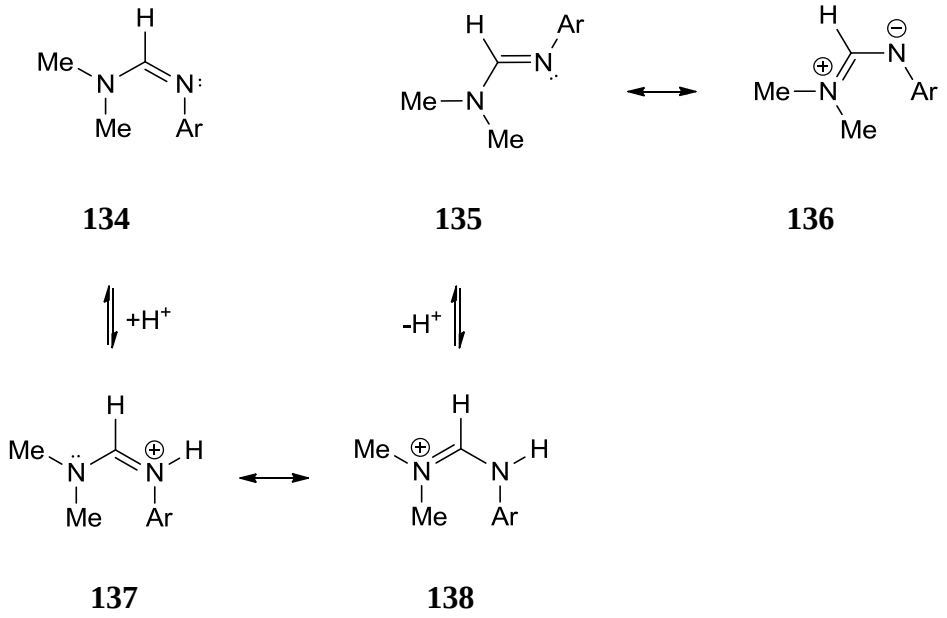
132 **133**

Figure 28: Amidine bases

Amidines are important functional groups in modern drug synthesis.[70] Oszczapowicz *et al.* chronicled the *ab initio* 3-21G optimisation of the molecular structures of fluoro derivatives of formamidines and their conjugate acids.[71] It was concluded that substituents at both nitrogen atoms would have an influence on the extent of conjugation along the amidine functionality. The proposal that electron-withdrawing substituents at the imino nitrogen atom would cause an increase in conjugation which would favour the resonance form (b), whereas electron-withdrawing substituents at the amino nitrogen would result in a decrease in conjugation and would therefore favour resonance form (a). Conversely, electron-donating groups at the imino nitrogen will favour the form (a) and at the amino nitrogen atom form (b)

will be favoured.[68h] From this, it was recognised that electron-withdrawing groups at the imino nitrogen should lead to an increase in the length of the formal C=N bond and a decrease in the length of the formal C-N bond and an overall decrease in basicity. These experimental results indicated that the fluoroformamidines studied were weaker bases than formamidines. It was also noted that the more basic the amidine, the larger the energy difference between the two tautomeric forms, where this property is possible for the amidine structures.

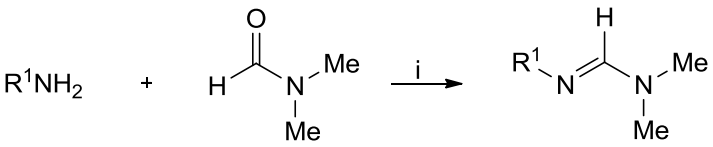
Hegarty *et al.* reported the isomerisation about the C-N and C=N bonds of E- and Z-amidines.[72] Heating the compounds in an inert solvent or treating with acid at room temperature resulted in complete isomerisation of **134** to **135** (Scheme 42).



Scheme 42: Isomerisation of amidines[72]

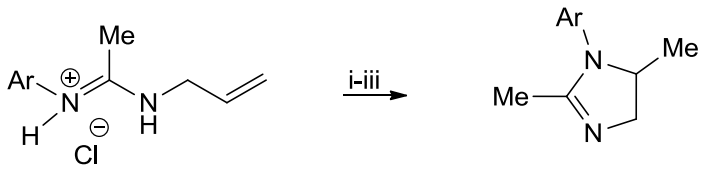
There are three sites in the amidino group to which substituents can be attached, the two nitrogen atoms and the amidino carbon atom.[68h] Substituents at both nitrogen atoms have considerable influence on the extent of conjugation. In general, '*the effects of a substituent at any site of the amidino group depends on substitution at the other two sites*'.

Cai and coworkers reported the use of arenesulfonylchlorides as coupling agents with DMF, which provided a one-step procedure for the synthesis of formamidines from primary amines (Scheme 43).[68i,73]



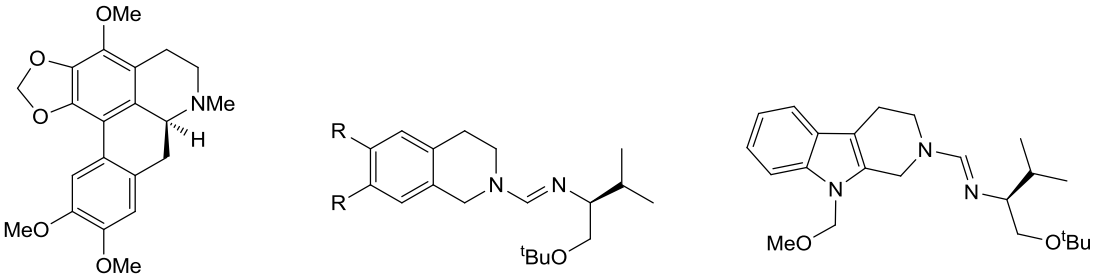
Scheme 43: Reagents: (i) $ArSO_2Cl$, r.t., <10min, 38-95%[68i,73]

Partridge *et al.* investigated the synthesis of cyclic amidines of the form 1-aryl-2,5-dimethyl-Δ^2-imidazoles (Scheme 44) from the *N*-allyl-*N´*-aryl-acetamidine hydrochloride.[74]



Scheme 44: Reagents: (i) 180-200 °C, 12 h, (ii) HCl, (iii) NaOH[74]

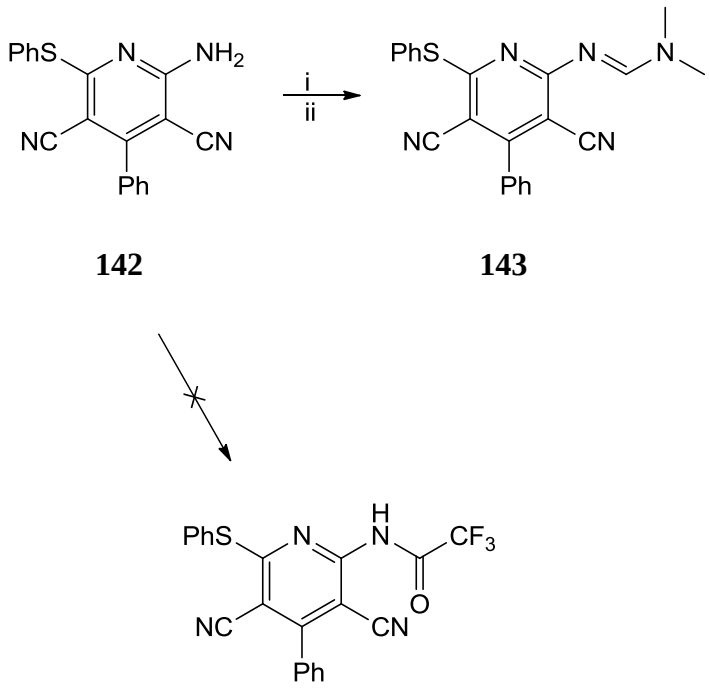
Meyers *et al.* demonstrated the asymmetric synthesis of (+)-ocoteine **139** *via* chiral formamidines containing the tetrahydroisoquinoline or *β*-carboline moieties **140** and **141** (Figure 29).[75]



139 **140** **141**

Figure 29: Chiral formamidines

Chen *et al.* used trifluoroacetic anhydride (TFAA) as a coupling agent in the synthesis of formamidines and regarded the method as a '*novel, convenient and highly efficient synthesis*'.[76] This method was in fact established when the intended modification of the amino group present in 2-amino-4-phenyl-6-phenylsulfonyl-pyridine-3,5-carbonitrile **142** didn't go according to expectation. Treating **142** with sodium hydride in DMF, which is both the solvent and a reagent (Scheme 45), followed by the addition of an equivalent of TFAA resulted in the formation of *N´*-(3,5-dicyano-4-phenyl-6-phenylsulfanyl-pyridin-2-yl)-*N*,*N´*-dimethylformamidine **143**, instead of the anticipated *N*-(3,5-dicyano-4-phenyl-6-phenyl-sulfanyl-pyridin-2-yl)-2,2,2-trifluoroacetamide **144**. The amidine **143** was isolated in high yield (93-100%).



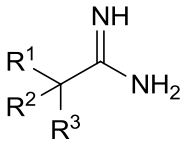
142 **143**

144

Scheme 45: Reagents: (i) NaH; (ii) TFAA, DMF[76]

3.1.1.1 Biological activity of amidines

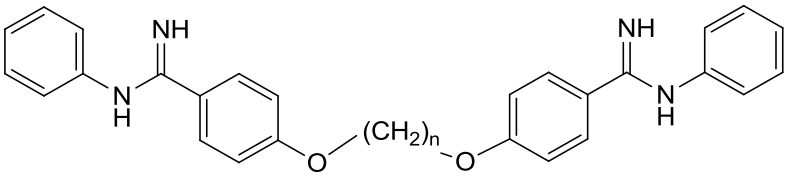
In the 1920s, Newbery and Webstertested *mono*-amidines **145** as bactericides against *M. Tuberculosum* (Figure 30).[77] Some of the amidines possessed anti-bacterial properties and marked *in vitro* activity against *M. tuberculosum*. Infections in the guinea pig were targeted as their biological test subjects and it was concluded that *mono*-amidines were regarded as being '*too toxic for the prolonged administration likely to be required to demonstrate activity against guinea pig infections*'.



145

Figure 30: *Mono*-amidine structure

Further developments in this area in the 1940s explored benzamidines as potential chemotherapeutic agents in the treatment of tuberculosis. Partridge found that *N*-aryl benzamidines such as **146** (where n = 2,3,4,5 or 6) showed high activity *in vitro*, however '*no activity could be demonstrated in vivo*'(Figure 31).[78]

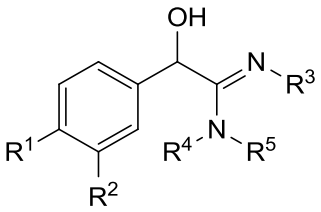


146

Figure 31: *N*-Aryl benzamidines

Many other research groups explored the activity of various amidines as potential anti-tuberculosis agents, thereby affording a substantial library of amidines and establishing routes to their synthesis.[78-79]

Bristow explored the potential use of mandelamidines as bronchodilators. Each of the compounds were isolated as their hydrochloride salts (**147, 148** and **149**) (Figure 32). None exhibited any bronchodilator properties.[80]



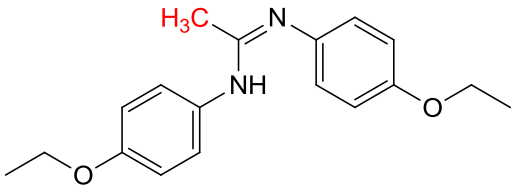
147 $R^1 = R^2 = R^3 = R^4 = R^5 = H$

148 $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = OH$

149 $R^1 = R^2 = OBn$, $R^3 = R^4 = R^5 = H$

Figure 32: Structure of mandelamidines

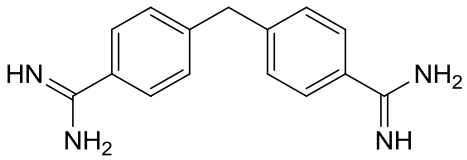
Hill *et al.* described the substituted amidine, Holocaine® **150**, as an analgesic (Figure 33).[81] In this publication, the synthesis of analogs of Holocaine® where the methyl (-CH_3) group was substituted by ethyl, *n*-propyl and *iso*butyl groups were explored in an effort to identify potential new analgesics.



150

Figure 33: Holocaine® 150

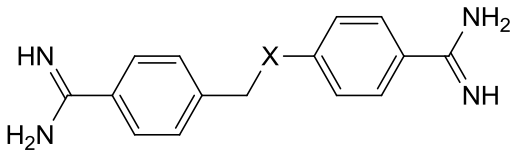
Self *et al.* explored the role of *bis*-amidine **151** as potential trypanocidal agents (Figure 34).[82] The trypanosomes in the blood stream were targetted and were used as a treatment against protozoan parasites of the type encountered in malaria infections.



151

Figure 34: *Bis*-Amidine

The homologue **152** showed a maximum activity coinciding with the disappearance of trypansomes from the peripheral blood stream (Figure 35).



152 X = CH_2

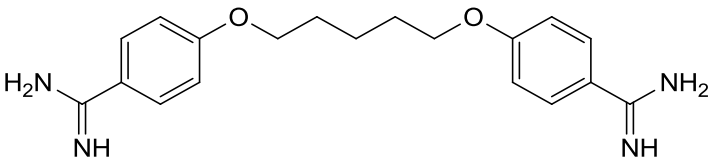
153 X = O

154 X = NH

155 X = S

Figure 35: The *bis*-amidine analogues examined as potential trypanocidal agents

Substitution of a methylene group by oxygen (Structure **153**) results in slightly improved activity. The aza-analogue **154** shows little change in activity relative to **152**. The sulfur analogue **155** is inactive. The best known *bis*-amidine is marketed as NebuPent® or Pentam® 300 and its active pharmaceutical ingredient (API) is pentamidine **156** (Figure 36). It is used in the treatment of *Pneumocystis pneumonia*.

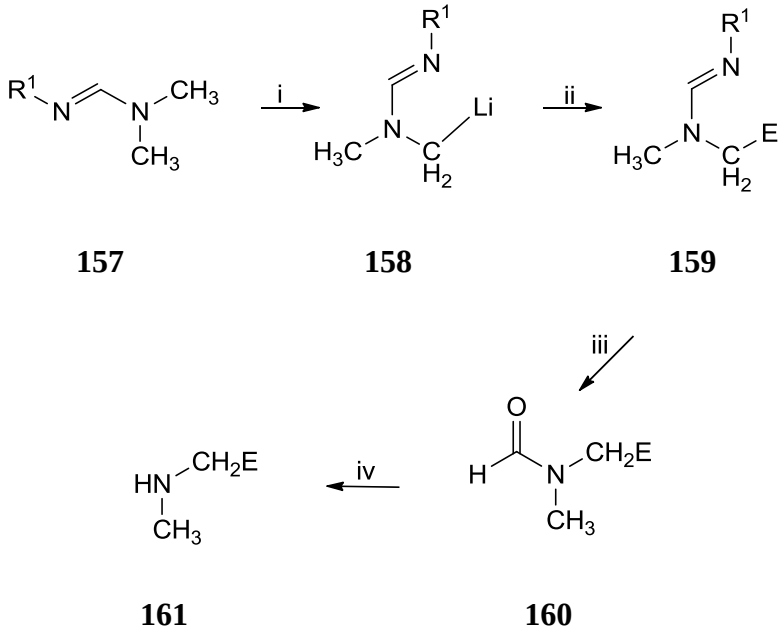


156

Figure 36: Pentamidine 156

3.1.1.2 Synthetic importance of amidines

Meyers *et al.* outlined the reduction of amidines in the generation of tertiary amines.[83] They proposed that an amidine can be regarded as '*generally useful precursor to α-substituted amines*'. Initially, the reaction proceded from the amidines **157** to **158** and then treatment with various electrophiles (E), such as MeI, *n*-PrI and cyclohexanone, resulted in the formation of the amidines **159**. Subsequent transformations lead to the *N*-formyl derivatives **160** and amines **161** (Scheme 46).



157 **158** **159**

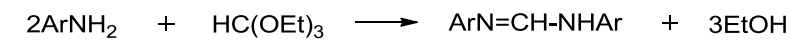
161 **160**

Scheme 46: Reagents: (i) ^{t}BuLi (1.1 equiv.), THF, -78 °C; (ii) -78 °C, electrophile; (iii) methanol-H_2O, 20 °C, 15 h; (iv) 5 equiv. KOH, 2:1 methanol-H_2O, reflux, H^+[83]

3.2 Synthesis of amidines

3.2.1 Synthesis from amines

De Wolfe investigated access to diarylamidines **164** *via* reaction of triethylorthoformate with primary amines (Scheme 47).[84]



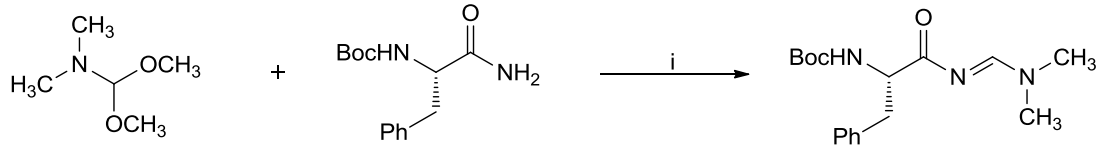
162 **163** **164**

Scheme 47: Reaction of triethylorthoformate with primary amines as a route to diarylamidines 164[84]

Further examination by Taylor *et al.* prompted the observation that '*when two moles of aromatic amine are present per mole of ortho-ester, an amidine is obtained whether acid is present or not*'.[85] When the amine was benzylamine, Taylor *et al.* isolated the amidine free base in 68% yield by adding benzylamine to a refluxing solution of triethylorthoformate and acetic acid and continuing to reflux for a further 2 h. Distillation followed by a workup which included a sodium bicarbonate wash afforded the title compound.

Sergheraert *et al.*[86] explored an alternative synthesis of amidines from amines using a coupling agent of the type usually employed in peptide synthesis, e.g. bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate (PyBroP). Reaction conditions involved one equivalent each of amine, PyBroP and *di*-isopropylethylamine which were reacted together in DMF for 5 h at room temperature. Following purification by HPLC or thick-layer chromatography, amidine yields of 42-77% were achieved. Other advantages to this method of synthesising formamidines includes (i) the mildness of reaction conditions and relatively short reaction times, (ii) the use of a commercially available coupling reagent which is easy to handle and (iii) the suitability of the reaction for both aliphatic and aromatic amines.

The reaction of an amine with an amide acetal has also been investigated.[87] Myers *et al.* investigated the use of *N*,*N*-dimethylformamide dimethylacetal **165** and observed the formation of *N*-acyl amidines from amides (Scheme 48).



165 **166** **167**

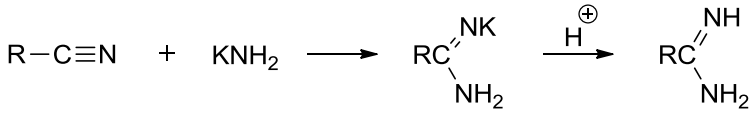
Scheme 48: Reagents: (i) 5A molecular sieves, CH_2Cl_2, 40 °C, 4 h[87]

3.2.2 Synthesis from nitriles

Additions of ammonia and amines to nitriles are only feasible for amidine production in the case of nitriles activated by electron-withdrawing substituents in the position *α*- to the C≡N bond.[68g] In practice three types of reactions are used.

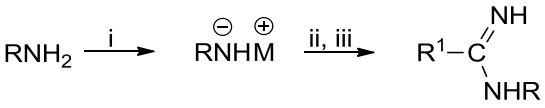
3.2.2.1 Addition of metal amides to nitriles

This type of reaction uses the metal derivatives of ammonia or of amines as nucleophiles. The interaction of alkali amide anions with nitriles involves the addition of sodium or potassium salts of amines to nitriles (Scheme 49). This generates metallic derivatives which in turn are converted into amidines by the action of the proton donors.[77,88]



Scheme 49: The interaction of alkali amide anions with nitriles[77,88]

The reaction of amide anions with nitriles is used in the preparation of monosubstituted amidines (Scheme 50). In one of the first reported methods, the metallation was brought about by the use of sodium metal. Cooper and Partridge studied this process in detail and reported yields up to 83%.[68e]



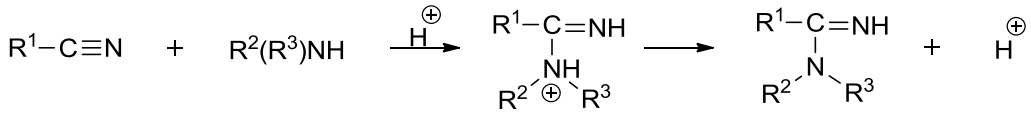
Scheme 50: Reagents: (i) Na; (ii) R^1CN; (iii) H_2O[68e]

During this reaction, care must be taken to ensure in the final hydrolysis step, that the metallated amidine is not converted to an amide.[89] The limitation of this process is that it is only useful in the formation of unsubstituted amidines.

Singh *et al.* identified an alternative to this method of generating a mono-substituted amidine.[90] The reaction conditions involved combining equimolar amounts of amine, nitrile and sodium hydride in DMSO and stirring the mixture in an icebath for 2-3 h, then at r.t. for several hours until reaction is complete (by t.l.c.). The resulting suspension is then poured onto ice water and the solid filtered and recrystallised from alcohol. The advantage of this method over others, is that it requires relatively mild conditions and produces high yields (85-89%) of the amidines.

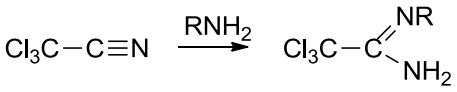
3.2.2.2 Addition of ammonium salts or amines to nitriles.

The addition of amines to nitriles is outlined in Scheme 51.



Scheme 51: The addition of amines to nitriles

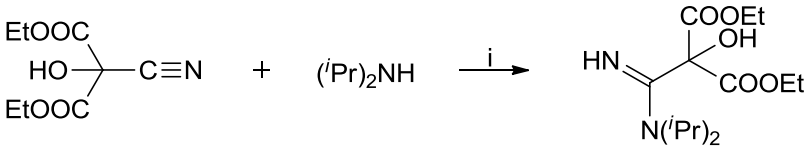
For the direct addition of ammonia and free amines to be carried out, the nitrile must be activated by electron-withdrawing groups on the α-carbon (Scheme 52).[91]



168

Scheme 52: Direct addition of ammonia and free amines to nitrile in the preparation of amidines[91]

Perfluoroalkyl nitriles (R_FC-C≡N, where R_F = C_3F_7 or C_2F_5) and ethyl cyanotartronate **169** are examples of nitriles which can be used in direct addition reactions of this type (Scheme 53).[91-92]

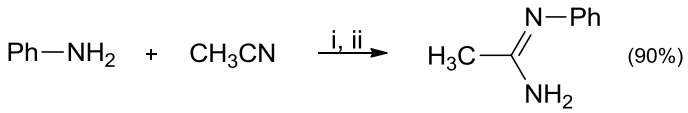


169 **170** **171**

Scheme 53: Reagents: (i) Diethyl ether, -17 °C[91-92]

Early studies on the addition of ammonium salts to nitriles by Cornell have been further developed by Partridge and Short and Schaefer and Krapcho.[68b,88,93] Partridge and Short explored the reaction of molten mixtures of nitriles with ammonium thiocyanate. Whereas Schaefer and Krapcho investigated decreasing the temperature and working with the ammonia under pressure. Of the ammonium salts surveyed, the hydrochlorides and bromides gave excellent yields.

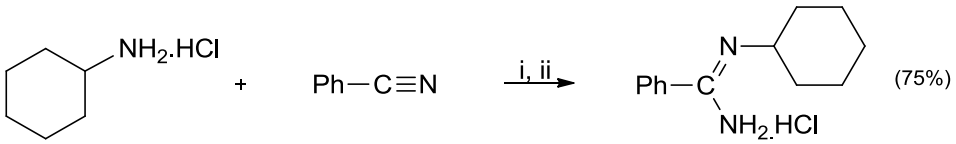
In the addition of amine hydrochloride salts to nitriles, satisfactory results were rarely obtained. The best results obtained in this approach are those illustrated by Cooper and Partridge (Scheme 54) and by Oxley *et al.* (Scheme 55).[68e,94]



172 **173**

Scheme 54: Reagents: (i) HCl, Diethyl ether, 1 month r.t. (ii) Base[68e,94]

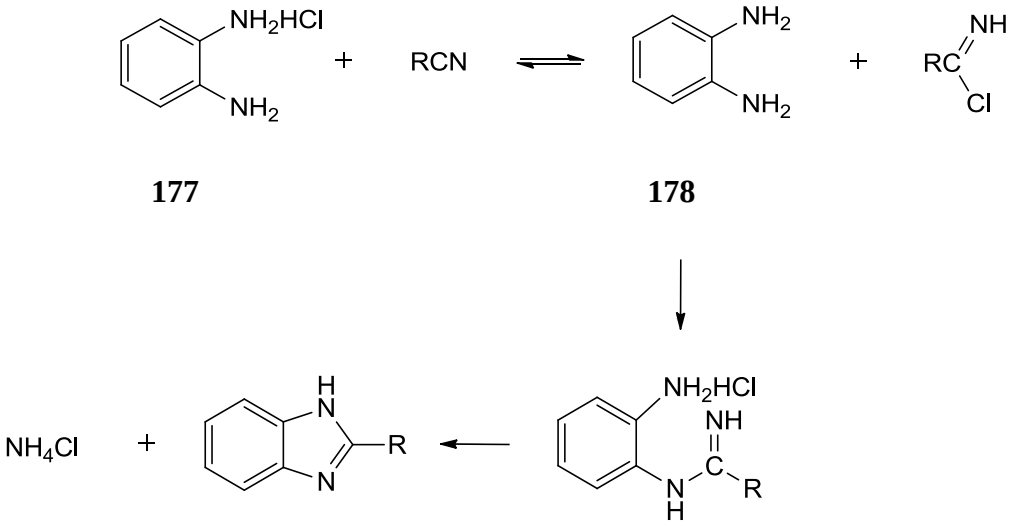
The addition of ammonium salts to nitriles is outlined in Scheme 55.



174 **175** **176**

Scheme 55: Reagents: (i) NH_4Cl, 180 °C, 8 h; (ii) 5N HCl

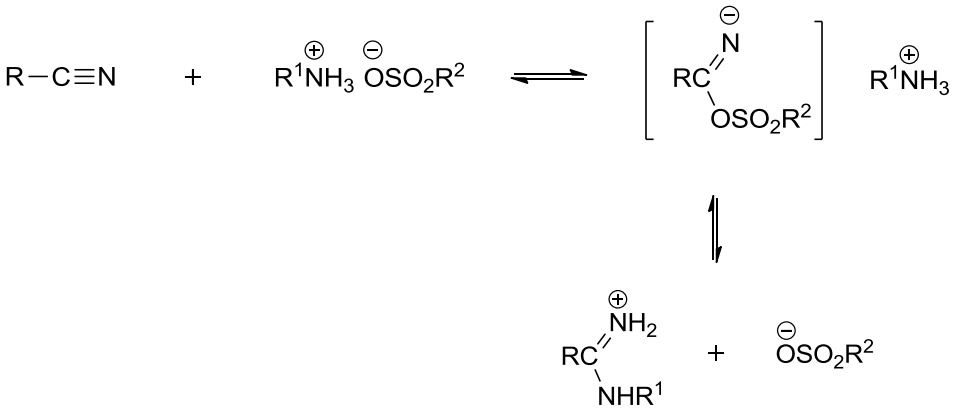
The formation of 2-substituted benzimidazoles was carried out by Hölljes and Wagner (Scheme 56).[95]



177 **178**

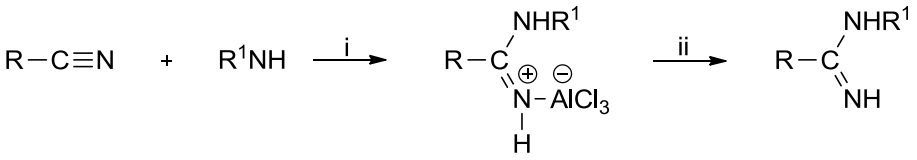
Scheme 56: The formation of 2-substituted benzimidazole[95]

The following is a scheme proposed by Oxley and Short for the reaction of ammonium arenesulfonates with nitriles (Scheme 57).[96] This method was successfully applied in the preparation of *mono*-arylamidines and cyclic amidines.[68d,79a,79c,79e]



Scheme 57: Preparation of *mono*-arylamidines and cyclic amidines[96]

Another route examined aluminium trichloride as a catalyst. It was anticipated that, '*catalysts of the Friedel Crafts type might enhance the dipole condition of the molecule and with it, its reactivity*'(Scheme 58).[97]

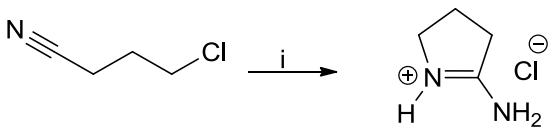


179 **180** **181** **182**

Scheme 58: Reagents: (i) $AlCl_3$, base; (ii) H_2O[97]

At the end of the reaction, the complex of the amidine and aluminium chloride was decomposed by water and the organic product isolated by recrystallisation.

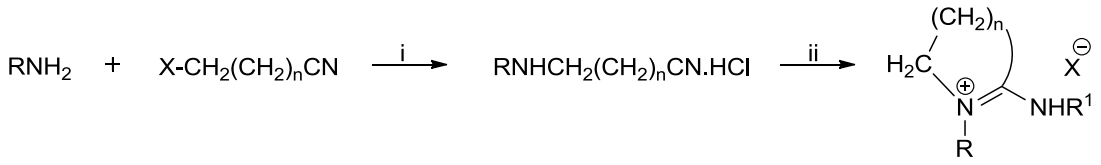
The preparation of cyclic amidines from γ-halonitriles was explored by Moriconi *et al*. with **183** successfully isolated in 50% yield (Scheme 59).[68f]



184 **183**

Scheme 59: Reagents: (i) excess NH_3[68f]

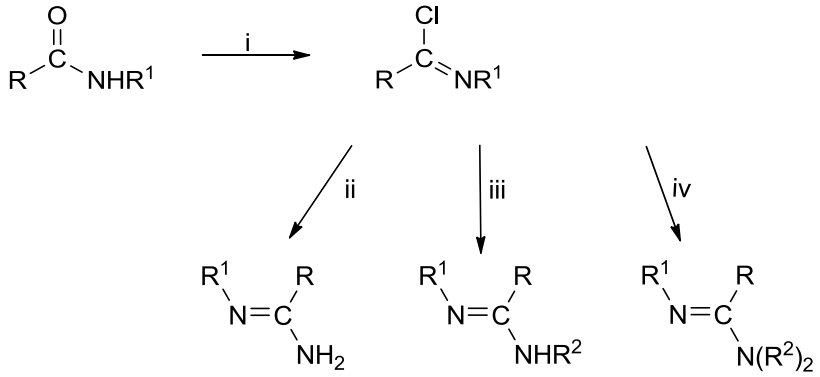
Experimental results outlined by Moriconi *et al.* support conclusions previously reported in the literature, they serve to correct older literature in the area and to expand the general reaction to other *ω*–halonitriles (Scheme 60).[98]



Scheme 60: Reagents: (i) autoclave, ethanol, 120 °C, 8h; (ii) aqueous workup[98]

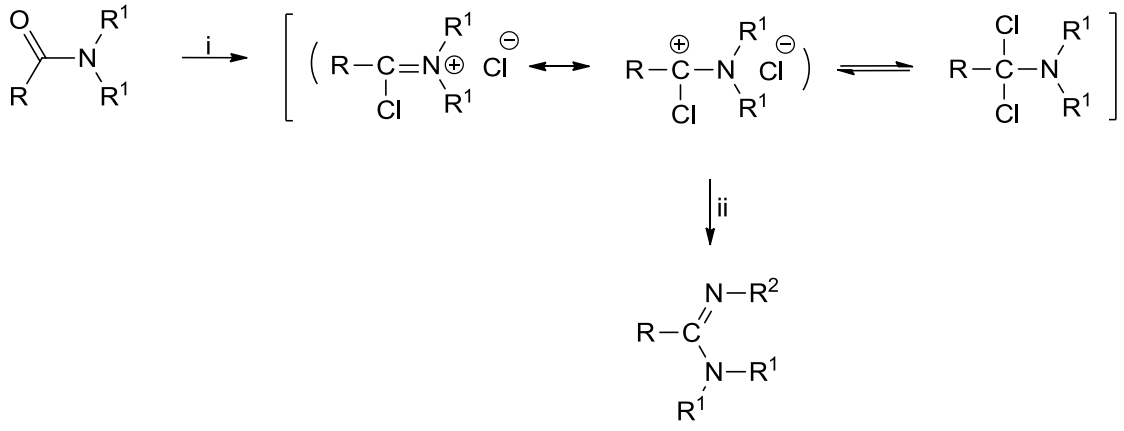
3.2.3 Preparation from amides

Amidines may be synthesised from amides by condensation with amines in the presence of halogenating agents. The coupling can be carried out in a variety of ways. For example, the reaction of *mono*-substituted amides with a halogenating agent results in the formation of an imidoyl halide. This imidoyl halide is then reacted with ammonia or with an amine to yield substituted amidines (Scheme 61).[68g]



Scheme 61: Reagents: (i) PCl_5, (ii) NH_3, (iii) R^2NH_2, (iv) $(R^2)_2NH$[68g]

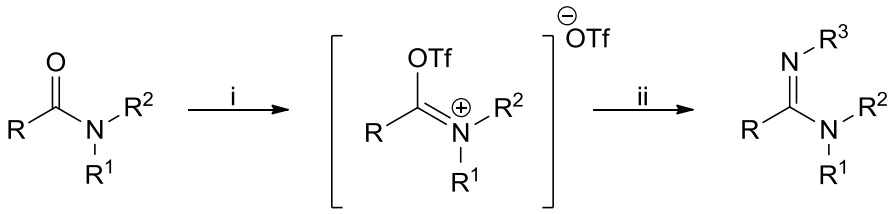
Synthesis of amidines from *N*,*N*-disubstituted amides proceeds *via* a dichloro derivative (Scheme 62).[68g]



Scheme 62: Reagents: (i) PCl_5, (ii) R^2NH_2[68g]

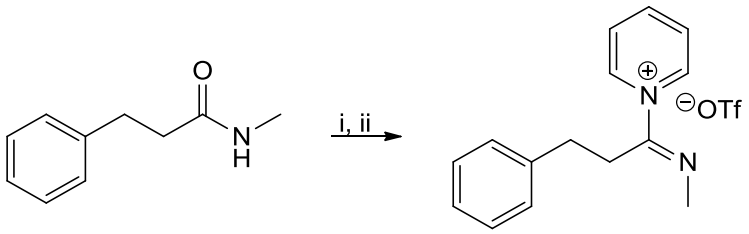
Charette *et al.* investigated the use of triflic anhydride to activate amides in their conversion into amidines (Scheme 63).[99] The protocol involved addition of triflic anhydride to a

secondary or tertiary amide which would generate the iminium triflate that would be converted into the amidine upon addition of the appropriate amine. Poor conversion was initially observed, but optimisation of the reaction which involved adding the amine as the hydrochloride salt gave amidines in isolable yields of up to 84%.



Scheme 63: Reagents: (i) Tf_2O, (ii) $R^3NH_2.HCl$[99]

Further mechanistic investigations outlined in Scheme 64 involved the isolation of 1-pyridylimidoyl triflate **185** which was isolated after a short reaction time (< 2 h).



186 **185**

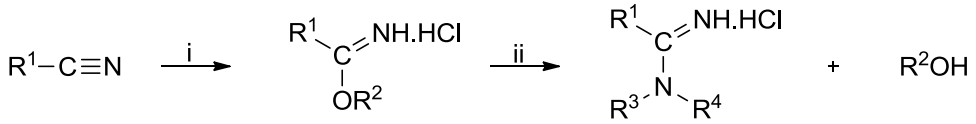
Scheme 64: Reagents: (i) CD_2Cl_2, pyridine, *α,α,α*-trifluorotoluene; (ii) Triflic anhydride, -40 °C[99]

3.2.4 Preparation from imidates

Neilson *et al.* reviewed the role of imidates in the synthesis of amidines.[100] A number of methods of synthesis of amidines from imidates are outlined below. However, the synthesis of amidines from imidates has been subject to some criticism as large volumes of anhydrous solvents are required to complete the procedure. Also other, more direct synthetic routes to amidines have been devised.[68b,c,96]

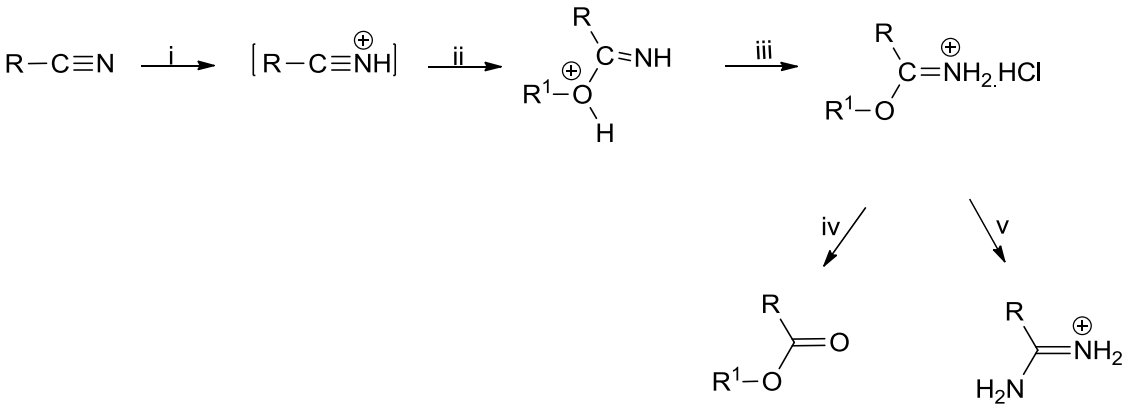
3.2.4.1 From imidoesters with ammonia or amines (Pinner synthesis)

The Pinner synthesis is a two-step reaction.[68g] The first involves transformation of nitriles into imido esters that are then converted into amidines. The iminoether hydrochloride is produced when the nitrile is treated with gaseous hydrogen chloride in a mixture of anhydrous chloroform and an alcohol (Scheme 65).



Scheme 65: Reagents: (i) HCl, R^2OH; (ii) $R^3(R^4)NH$[68g]

The salt produced is referred to as the Pinner salt and may react further with a nucleophile (Scheme 66).

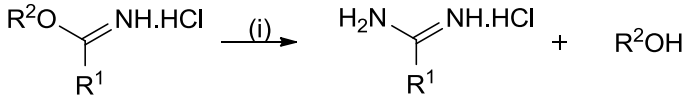


Scheme 66: Reagents: (i) H^+, (ii) R^1OH, (iii) HCl, (iv) H_2O, (v) NH_3[68g]

Pinner's method is used for the preparation of unsubstituted amidines. It is less successful for substituted amidines.

3.2.4.2 Reaction of imidates with ammonia and substituted amines

Neilson *et al.* illustrated the reactions of imidates with ammonia and substituted amines in the formation of amidines.[100] Firstly, the reactions of imidate salts with alcoholic ammonia solutions were explored (Scheme 67).



Scheme 67: Reagents: (i) NH_3[100]

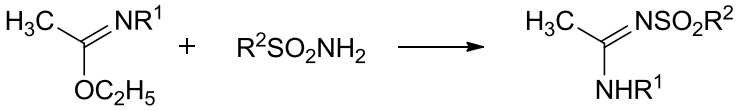
Heating imidates with ammonium salts in aqueous alcohol at 50-70 ^oC was found to yield amidines (Scheme 68).[100]

Scheme 68: Reaction of imidates with ammonium salts[100]

Schaefer *et al.* also explored this method of preparation with commendable amidine yields (65-96%).[101]

3.2.4.3 Reaction of imidates with sulfonamides

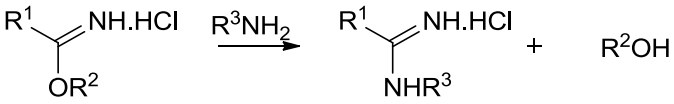
The reaction of imidates with sulfonamides in the preparation of amidines is outlined in Scheme 69.



Scheme 69: Reaction of imidates with sulfonamides[100]

3.2.4.4 Reaction of imidates with primary amines

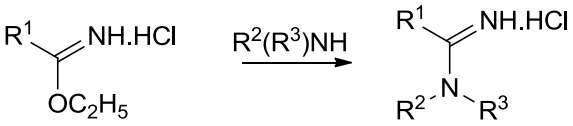
Imidate salts condense with primary amines to produce monosubstituted amidines (Scheme 70).



Scheme 70: Condensation of imidate salts with primary amines[100]

3.2.4.5 Reaction of imidates with secondary amines

Unsymmetrical disubstituted amidines are formed in the reaction of imidate salts with secondary amines (Scheme 71). Imidates do not react with tertiary amines to produce amidines.

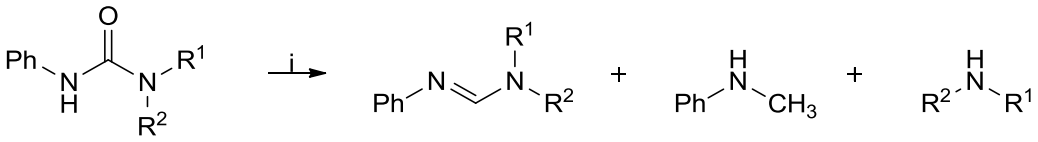


Scheme 71: Preparation of unsymmetrical disubstituted amidines[100]

3.2.5 Preparation from ureas

Larizza *et al.* explored the reduction of ureas as a route to formamidines. Such reactions were accompanied with the formation of amine side-products (Scheme 72).[102] The standard reaction conditions involved refluxing the urea with $LiAlH_4$ in a 1:1 solution of

benzene:ether. Following an aqueous workup, the aqueous phase was made alkaline with potassium carbonate and extracted with diethyl ether. The resulting residue on evaporation was purified by distillation. When *N*-butylureas (R^1 = nC_4H_9) were used, the disubstituted *N*-butylformamidines were isolated in yields ranging from 28-53%. With phenylureas (R^1 = Ph), *N*-phenylformamidines yields ranged from 29-62%. Varying the reflux time and urea to reducing agent molar ratios aided in reducing the amine side products. As a general observation, it was initially noted that the standard conditions were too harsh for phenylureas resulting in increased quantities of amine side products. In the case of the 1,1-dialkyl-3-butylureas, the conditions were too mild as the majority of the reaction material isolated was the urea starting material.

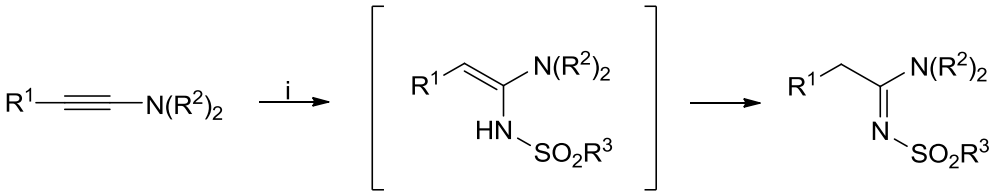


187a	$R^1 = R^2 = CH_3$	**188a**	$R^1 = R^2 = CH_3$	**189**	**190a** $R^1 = R^2 = CH_3$
187b	$R^1 = R^2 = C_2H_5$	**188b**	$R^1 = R^2 = C_2H_5$		**190b** $R^1 = R^2 = C_2H_5$
187c	$R^1 = CH_3$, $R^2 = C_6H_{11}$	**188c**	$R^1 = CH_3$, $R^2 = C_6H_{11}$		**190c** $R^1 = CH_3$, $R^2 = C_6H_{11}$

Scheme 72: Reagents: (i) $LiAlH_4$, ether : benzene (1:1)[102]

3.2.6 Preparation from ynamines

Kuehne *et al.* investigated the synthesis of arylsulfonylamidines from ynamines (Scheme 73).[103] The product *N*-*p*-toluene-sulfonyl-*N´*,*N´*-diethylphenylacetamidine **193a** was isolated in 80% yield.



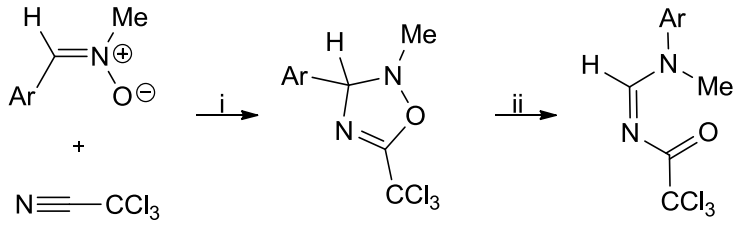
191 **192** **193**

193a	$R^1 = C_6H_5$, $R^2 = C_2H_5$, $R^3 = CH_3C_6H_4$
193b	$R^1 = n\text{-}C_5H_{11}$, $R^2 = n\text{-}C_3H_7$, $R^3 = CH_3C_6H_4$
193c	$R^1 = n\text{-}C_5H_{11}$, $R^2 = C_2H_5$, $R^3 = Ph$

Scheme 73: Reagents: (i) $R^3SO_2NH_2$[103]

3.2.7 Preparation of amidines *via* rearrangement of Δ⁴-1,2,4-oxadiazolines

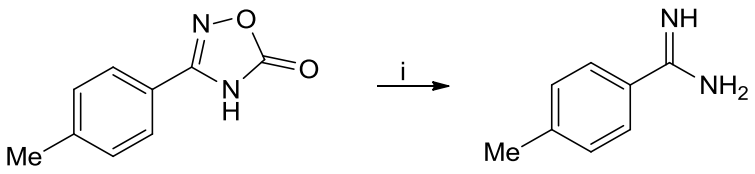
Wagner *et al.* synthesised Δ^4-1,2,4-oxadiazolines *via* the 1,3-dipolar cycloaddition of nitrones with trichloroacetonitrile.[104] These Δ^4-1,2,4-oxadiazolines in turn underwent a rearrangement *via* ring opening and a 1,2-aryl shift from carbon to the adjacent nitrogen to yield formamidine derivatives (Scheme 74). The aryl substituents explored in this work were *mono-*, *di-* and *tri*-methoxyphenyl groups.



194

Scheme 74: Reagents: (i) 60 °C, 1 h – 4 d; (ii) 60 °C, 12 h – 70 d[104]

3-Substituted-1,2,4-oxadiazolin-5-ones **195** are described by Coote *et al.* as being useful amidine precursors and masked amidines. Hydrogenation of the oxadiazoline afforded the amidine **196** (Scheme 75).[105]



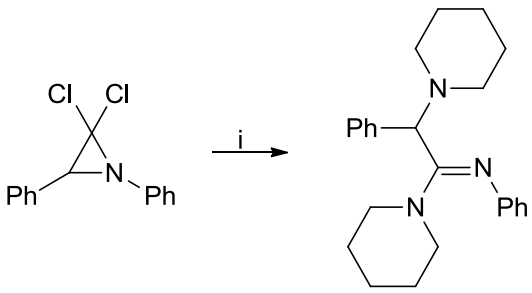
195 **196**

Scheme 75: Reagents: (i) H_2, Pd/C, ethyl acetate, AcOH, 20 h (91% yield)[105]

In the same paper, Coote *et al.* promoted the use of 1,2,4-oxadiazolin-5-ones as masked amidines for *N*-alkylated amidines as they are base stable and would be easily cleaved under mild conditions.

3.2.8 Preparation from *gem*-dichloroaziridines

Meilahn *et al.* established that the aminolysis of *gem*-dichloroaziridines provided a new and convenient synthesis of amidines.[106] This was achieved by dissolving the *gem*-dichloroaziridine **197** in the amine (piperidine) and heating the resulting solution slowly to 100-130 ^{o}C and maintaining the solution at this temperature for several hours (Scheme 76).



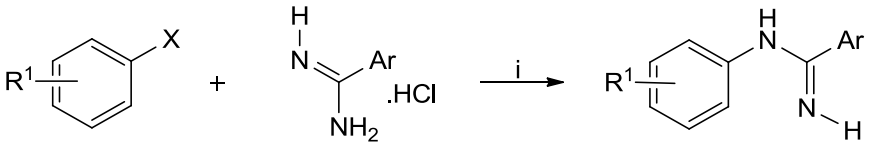
197 **198**

Scheme 76: Reagents: (i) Piperidine, 100-130°C[106]

The piperidine hydrochloride is easily removed by filtration or aqueous work-up. Crystallisation affords the amidine in yields varying from 36 to 74%. *Gem*-dichloraziridines are easily accessed *via* the addition of dichlorocarbene (generated by the action of sodium methoxide on chloroform) to *N*-benzylideneaniline.

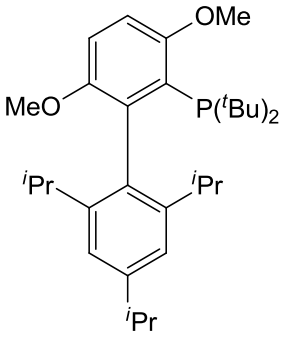
3.2.9 Preparation *via N*-monoarylation of aryl amidines

Buchwald *et al.* explored the development of a method for palladium catalysed *N*-arylation of both aryl and alkyl amidines (Scheme 77).[70]



Scheme 77: Reagents: (i) Pd_2dba_3 (0.25 – 2.5 mol%), 199 (1.0 – 10.0 mol%), Cs_2CO_3, *t*-butanol[70]

Using a biaryl phosphine ligand **199**, the preparation of *N*-aryl amidines in almost quantitative yields was achieved (Figure 37).



199

Figure 37: Biaryl phosphine ligand

It was noted that the particle size of the Cs_2CO_3 was crucial for successful conversion with the ligand **199**. When the base was ground using a mortar and pestle, the conversion rates consistently increased. A range of aryl formamidines could be coupled with a wide variety of aryl bromides, chlorides and triflates in short reaction times (2h). Both bromides and triflates were found to be excellent substrates with successful conversion (R^1 = Me, 84 - 93%) using just 0.5 mol% Pd at 85 ^oC.

4 Oxadiazolines

Oxadiazolines are five-membered heterocycles containing one oxygen, two nitrogen and two carbon atoms, which can also be described as dihydro-oxadiazoles. Their exact structure is denoted by a nomenclature in which the oxygen atom is assigned position-1 on the ring. This ring also contains a single π-bond, the location of which is indicated by delta (Δ) notation (Figure 38).

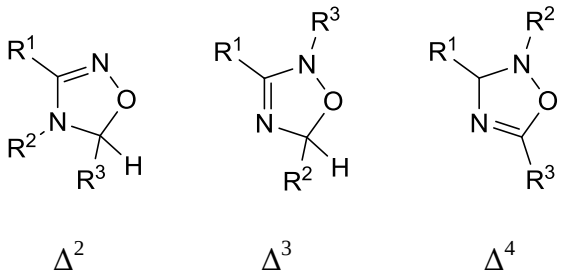
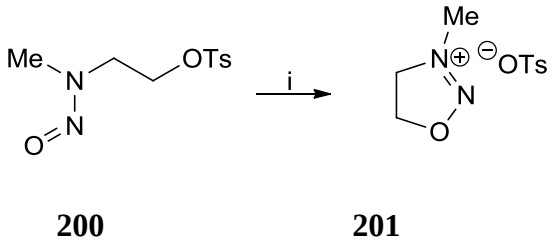


Figure 38: 1,2,4-Oxadiazolines

4.1 Δ²-1,2,3-Oxadiazolines

Gilchrist and O'Neill reviewed 1,2,3-oxadiazoles at length.[107] However, literature on Δ^2-1,2,3-oxadiazolines is limited. Koepke *et al.* prepared 4,5-dihydro-3-methyl-1,2,3-oxadiazolium tosylate **201** from *N*-nitroso-*N*-methyl-*N*-tosylamine **200** by just heating **200** in dichloromethane (Scheme 78).[108]

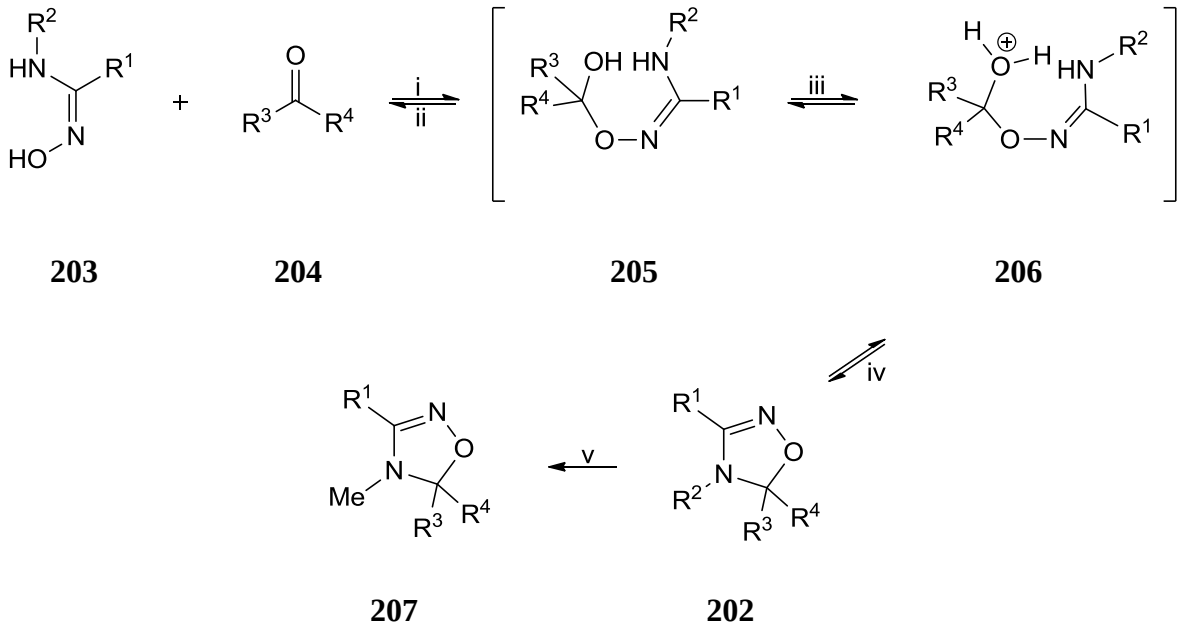


200 **201**

Scheme 78: Reagents: (i) Heat, CH_2Cl_2[108]

4.2 Δ^2-1,2,4-Oxadizolines

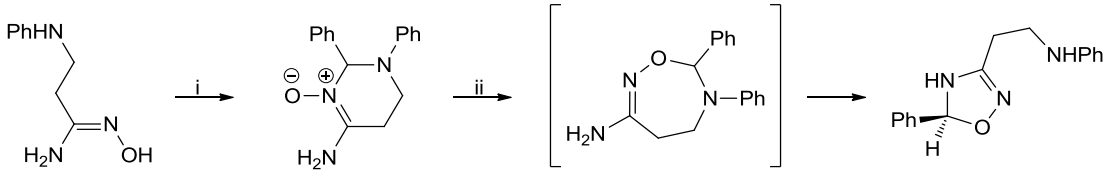
In 1889, Tiemann reported the first synthesis of a 1,2,4-oxadiazoline derivative *via* cyclocondensation of benzamidoxime with acetaldehyde.[109] A general method for the preparation of Δ^2-1,2,4-oxadiazolines involves the condensation of amidoximes with aldehydes or ketones.[110] This reaction is reversible on treatment with aqueous acid. The oxadiazolines **202** are hydrolysed to the carbonyl compounds and the amidoximes **203** (Scheme 79).



203 **204** **205** **206** **207** **202**

Scheme 79: Reagents: (i) neat or H_2O or AcOH; (ii) 23 °C, reflux, 2 h – 20 d, 30-80%; (iii) H^+; (iv) $-H_2O$, $-H^+$; (v) liq. $NH_3/NaNH_2$, MeI/diethyl ether, R^1, R^3 = H, 100%[110]

Oxadiazolines such as **202** (R^2 = H) can be methylated or benzylated at N-4 to give **207**. Simon *et al.* noted that nitrone **209** rearranged under the influence of heat to form the oxadiazoline **211**, *via* the transient intermediate **210** (Scheme 80).[111]

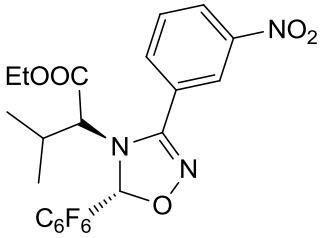


208 **209** **210** **211**

Scheme 80: Reagents: (i) PhCHO, methanol; (ii) Toluene or Ethanol or H_2O, 70-95 °C, 4-5 h, >90%[111]

Zhu *et al.* explored sodium bicarbonate and triethylamine as dehydrohalogenating agents in the synthesis of Δ^2-1,2,4-oxadiazolines from *p*-bromobenzohydroximoyl chloride and an

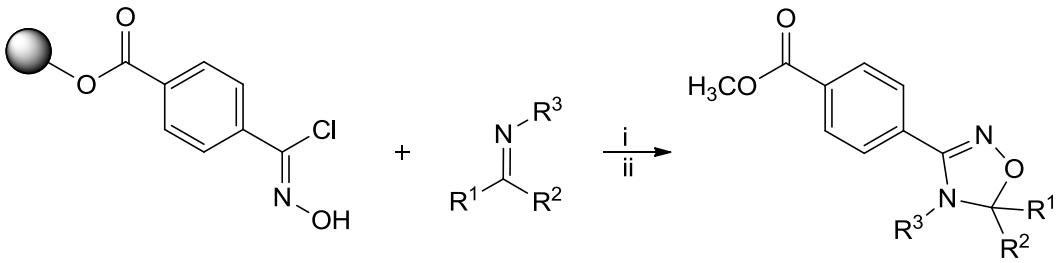
imine.[29] Compared with triethylamine, using sodium bicarbonate reduced the time of reaction from 3 days to 1 day in the synthesis of Δ^2-1,2,4-oxadiazoline **212** (Figure 39). An improved yield, from 56-90% in some cases, was noted.



212

Figure 39: Δ^2-1,2,4-Oxadiazoline

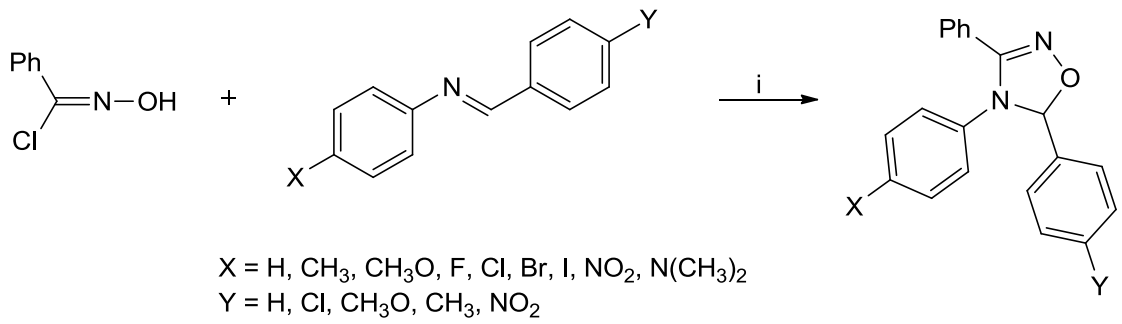
Wang *et al.* investigated the solid phase synthesis of Δ^2-1,2,4-oxadiazolines *via* the 1,3-dipolar cycloaddition of resin bound nitrile oxide with a variety of imines in a one pot reaction(Scheme 81).[112] At first, the Merrifield resin was chosen to initiate the study in a one-pot reaction.[112a] However, polyethylene glycol (PEG) was found to be soluble in a number of common solvents such as THF, DCM and water and therefore became the resin of choice.[112b,c]



213

Scheme 81: Reagents: (i) Trioctylamine, r.t.; (ii) CH_3ONa, CH_3OH, r.t.[112]

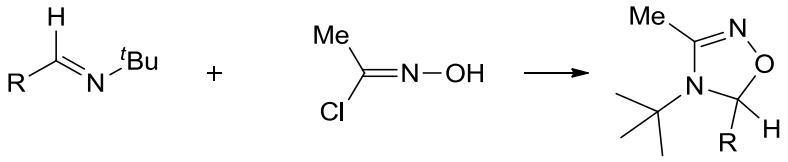
Orbital control in the 1,3-dipolar cycloaddition of benzonitrile oxide to benzylidene anilines was considered by Alcaide *et al.* (Scheme 82).[113] Benzonitrile oxide was generated *in situ* by the reaction of triethylamine on benzohydroximoyl chloride in the presence of two equivalents of the imine dipolarophile. This provided an excellent synthetic route to Δ^2-1,2,4-oxadiazolines.



26

Scheme 82: (i) Triethylamine, r.t.[113]

Clapp articulated that the best method of synthesising Δ^2-1,2,4-oxadiazolines was to carry out the cycloaddition of aliphatic or aromatic nitrile oxides with Schiff bases (Scheme 83).[114]

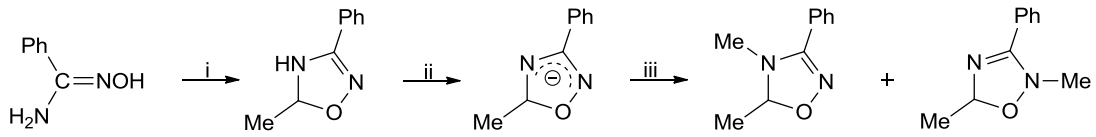


214

Scheme 83: The cycloaddition of aliphatic or aromatic nitrile oxides with Schiff bases in the preparation of Δ^2-1,2,4-oxadiazolines[114]

4.3 Δ^3-1,2,4-Oxadiazolines

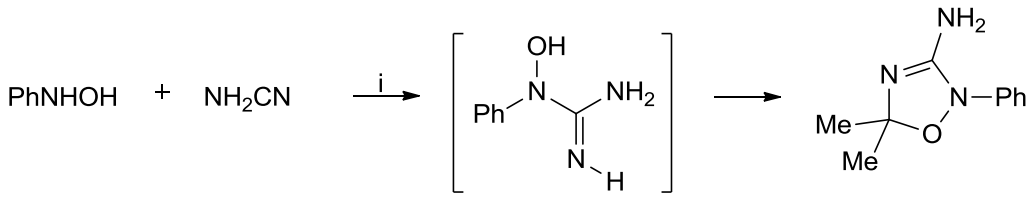
During the 1960s, benzamidoxime was the reagent of choice for Barrans and co-workers in the synthesis of Δ^2- and Δ^3-oxadiazolines (Scheme 84).[115] By removing the hydrogen on the N-4 in the Δ^2-oxadiazoline **216**, the anion **217** was generated. This anion was then alkylated using methyl iodide to give a 1:1 mixture of 3-phenyl-4,5-dimethyl- Δ^2-oxadiazoline **218** and the Δ^3-oxadiazoline **219**.



215 **216** **217** **218** **219**

Scheme 84: Reagents: (i) MeCHO, Diethyl ether; (ii) $NaNH_2$, $NH_{3(l)}$; (iii) MeI[115]

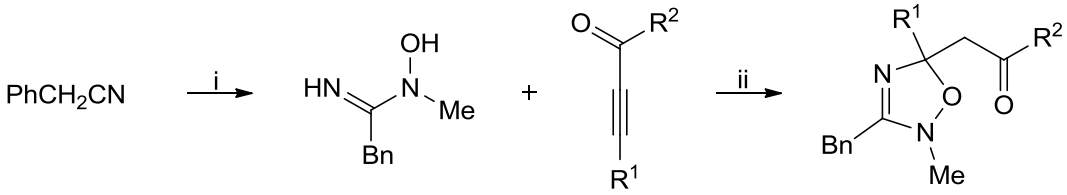
Hull and Farrand refluxed cyanamide with phenylhydroxylamine in acetone with the expectation of producing the disubstituted hydroxylamine **222** (Scheme 85).[116] Instead 3-amino-5,5-dimethyl-2-phenyl-3-oxadiazoline **223** was isolated.



220 **221** **222** **223**

Scheme 85: Reagents: (i) Acetone, hot $HCl_{(aq)}$[116]

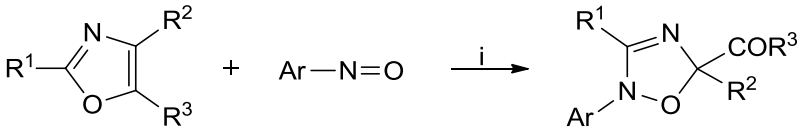
More recently in 2005, Naidu *et al.* described a one-pot synthesis of Δ^3-1,2,4-oxadiazolines from a nitrile in an aqueous solution.[117] The formation of oxadiazolines **224** in this manner involved a sequential double Michael addition of amidoximes to an electron-deficient alkyne (Scheme 86).



225 **226** **227** **224**

Scheme 86: Reagents: (i) MeNHOH.HCl, EtOH/H_2O, Na_2CO_3, 80 °C, 2 h; (ii) r.t.[117]

Ibata *et al.* demonstrated the cycloaddition of oxazoles **228** with nitrosoarenes **229** in the synthesis of 1,2,4-oxadiazolines **230** (Scheme 87).[118]



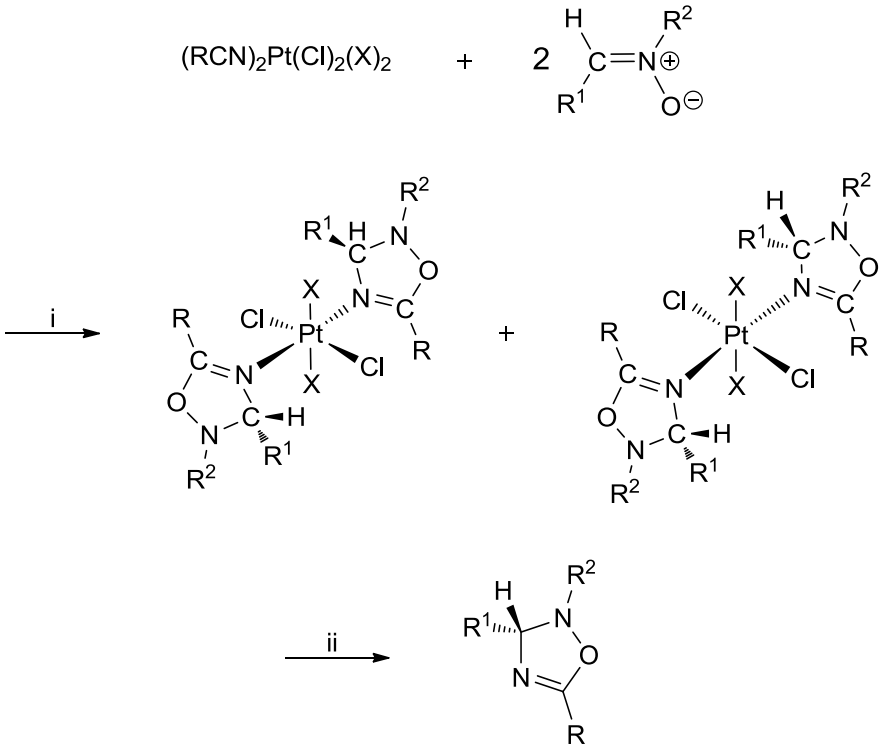
228 **229** **230**

Scheme 87: Reagents: (i) CH_3CN, r.t.[118]

4.4 Δ^4-1,2,4-Oxadiazolines

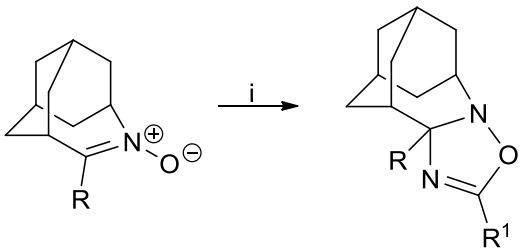
A variety of methods have been employed such as the platinum (IV)-assisted [2+3]-cycloaddition of nitrones to nitriles (Scheme 88) to yield co-ordinated platinum Δ^4-1,2,4-oxadiazolines (X = Cl).[119] These organic ligands can be easily liberated by reaction of the (Δ^4-1,2,4-oxadiazoline)platinum(IV) complexes with a slight excess of pyridine in chloroform (Scheme 88). The *trans*-[$PtCl_4$(pyridine)$_2$] formed which is highly insoluble in $CHCl_3$ and is

separated from the mixture by filtration. Evaporation of the solvent allowed isolation of the mixture of Δ^4-1,2,4-oxadiazolines to be obtained.



Scheme 88: Reagents: (i) DMSO, 50 °C overnight; (ii) Py, $CHCl_3$[119]

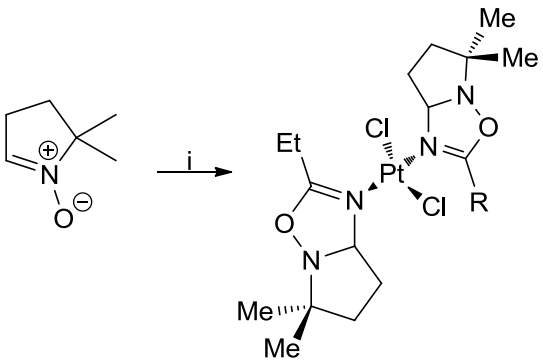
The 1,3-dipolar cycloaddition of nitriles to nitrones **231** in mild conditions has been investigated in the synthesis of Δ^4-1,2,4-oxadiazolines **232** and the corresponding Δ4-1,2,4-oxadiazoline complexes have been isolated in 68-83% yield (Scheme 89).[119b,120]



231 **232**

Scheme 89: Reagents: (i) R^1CN, Δ, 10kbar[120a]

Bicyclic Δ^4-1,2,4-oxadiazolines have been synthesised by reacting non-aromatic cyclic nitrones with alkylnitrile-Pt(II) complexes under mild conditions (Scheme 90).[121] Liberation of the heterocycle from the complex has yet to be achieved.

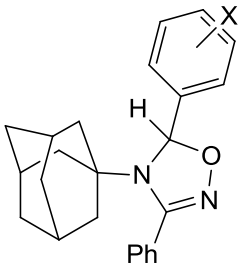


233

Scheme 90: Reagents: (i) $[(EtCN)_2Pt(Cl)_2]$, CH_2Cl_2:EtCN (1:1)[121]

4.4.1 Biological activity of Δ²-1,2,4-oxadiazolines

Carotti *et al.* and Monforte *et al.* recognised Δ^2-1,2,4-oxadiazolines for their anti-HIV activity.[122] Monforte *et al.* investigated the synthesis and *in vitro* anti-HIV activity of Δ^2-1,2,4-oxadiazoline (**234**, X = H), whereas Carotti *et al.* chronicled a library of Δ^2-1,2,4-oxadiazolines of the same structure with various substituents in the C-5 aryl ring (Figure 40).

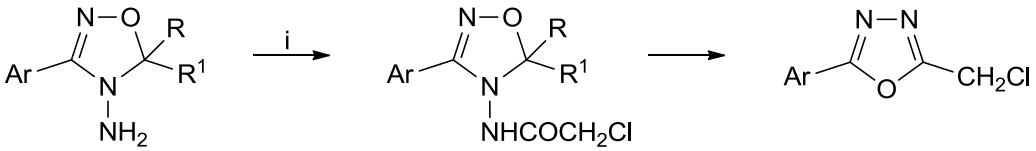


234

Figure 40: Δ^2-1,2,4-Oxadiazolines

The antitumour acitvity of these substituted Δ^2-1,2,4-oxadiazolines was investigated by Chimirri *et al*. who found that '*most of these compounds exhibit a wide range of inhibitory activity*' against a range of human tumour cell lines.[123]

El-Abadelah *et al.* investigated oxadiazolines with herbicidal action (Scheme 91).[124] This investigation sought to increase the herbicidal action of Δ^2-1,2,4-oxadiazolines. Findings from the study showed that introducing a chloroacetyl grouping at the *N*-4-amino functionality could help enhance the herbicidal action of the oxadiazolines. However, when using chloroacetyl chloride or chloroacetic anhydride to introduce the chloroacetyl group, the oxadiazoline itself underwent a transformation to 1,3,4-oxadiazoles **235**.

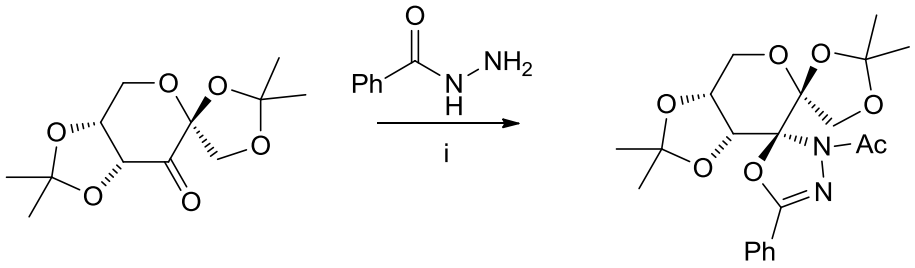


235

Scheme 91: Reagents: (i) $ClCH_2COCl$ or $(ClCH_2CO)_2O$[124]

4.5 Δ²-1,3,4-Oxadiazolines

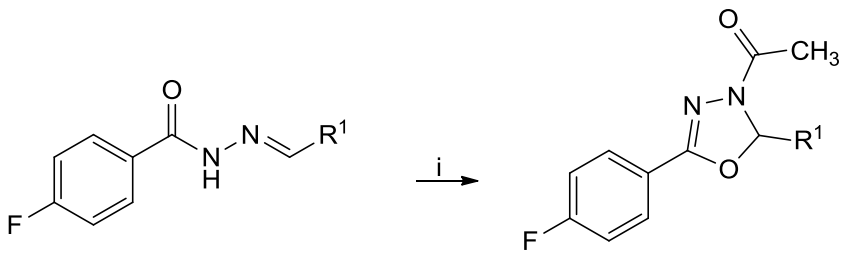
Yu *et al.* explored the preparation of a novel spiroheterocyclic oxadiazoline **237**, with a spiral junction at C-3 of fructopyranose group (Scheme 92).[125] This was achieved by reacting the pyranose derivative **236** with benzoylhydrazine affording the 3-benzoyl hexulopyranose oxadiazoline **237**.



236 **237**

Scheme 92: Reagents: (i) Methanol, Acetic acid, 60-65 °C, 6 h[125]

The drive to synthesise of Δ^2-1,3,4-oxadiazolines appears to be driven by the potential biological activity of the resulting structures. Rollas *et al.* investigated 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines as potential antimicrobial agents and isolated the 1,3,4-oxadiazolines (R^1 = *p*-NO_2Ph, *m*-NO_2Ph, 2,4-dinitrophenyl) **239** from the reaction of *N*-4-fluorobenzoyl hydrazones **238** with acetic anhydride (Scheme 93).[126]

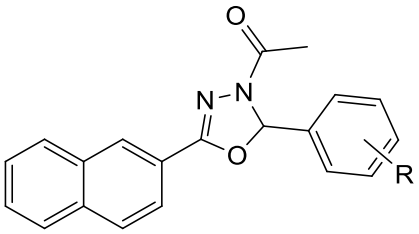


238 **239**

Scheme 93: Reagents: (i) Acetic anhydride[126]

When the antimicrobial activities of the hydrazones and 1,3,4-oxadiazolines were evaluated against *Staphylococcus aureus*, *Eschericha coli*, *Pseudomonas aeruginosa* and *Candida albicans*, it was evident that cyclisation of hydrazones into their corresponding 3-acetyl-1,3,4-oxadiazolines resulted in a decrease in antimicrobial activity against *S. aureus* strains.

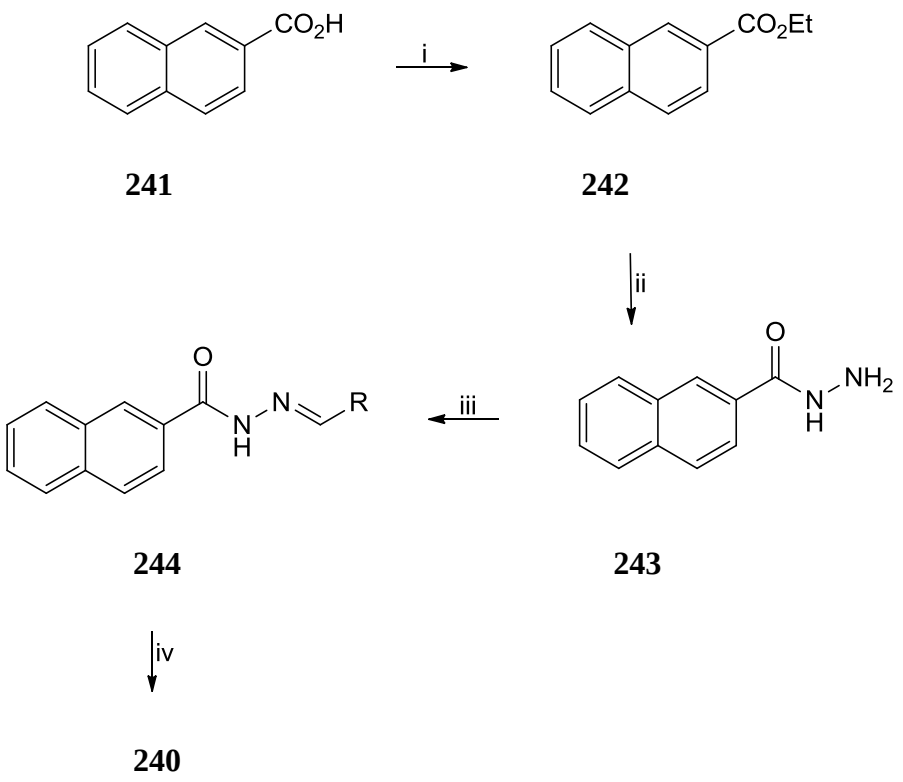
Retaining the geometrical features of combrestatin, a natural antimitotic agent, was the aim for Zhu *et al.*, who explored the formation of Δ^2-1,3,4-oxadiazolines such as **240** (R = Ph, *p*-NO_2Ph, *p*-Tolyl) (Figure 41).[127] It was envisaged that the oxadiazoline moiety would provide an optimal conformation for interaction with colchicine binding sites.



240

Figure 41: Δ^2-1,3,4-Oxadiazolines

Twenty analogues of oxadiazoline **240** were synthesised using the chemistry outlined in Scheme 94 and yields reached 86%.



Scheme 94: Reagents: (i) EtOH, H_2SO_4, reflux 8-12 h; (ii) N_2H_4-H_2O (85%), EtOH, reflux 8-12 h; (iii) EtOH, water, acetic acid, reflux, 5 h; (iv) $(Ac_2)O$, reflux, 1 h[127]

Incorporation of a pyrazole and an oxadiazoline moiety in a molecule offers the potential '*to develop new organic antibacterial activity compounds*'.[128] Yang *et al.* synthesised a range of compounds containing both the pyrazole and oxadiazoline groups (e.g. R^1 = OCH_3 and R^2 = NO_2) and found that these *bis*-heterocyclic compounds **245** displayed better fungicidal activity than pyrazole carbohydrazide hydrazone derivatives such as **246** (Figure 42).

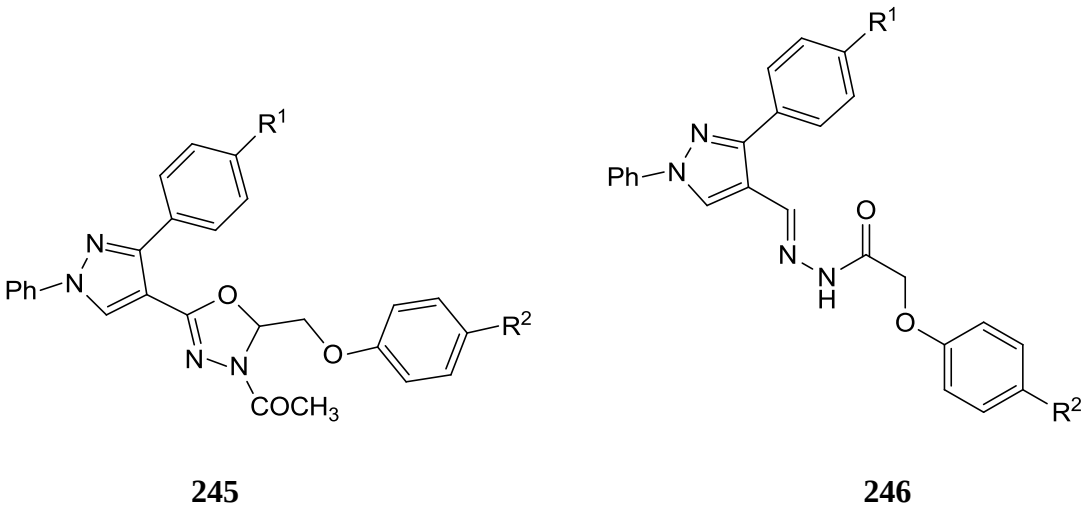
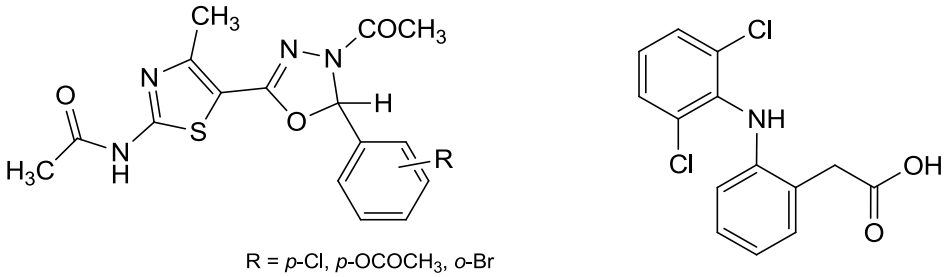


Figure 42: Pyrazole containing compounds 245 and 246

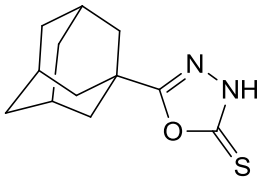
Thiazolyl-Δ^2-1,3,4-oxadiazolines **247** have been shown by Oniga *et al.* to have good anti-inflammatory potential when compared with the commercially available Diclofenac **248** (Figure 43).[129]



247 **248**

Figure 43: Compounds with potential anti-inflammatory properties

Similarly to Carotti *et al.*, and El-Emam *et al.* investigated the effect of an adamantyl group attached to the oxadiazoline moiety on antimicrobial and anti-HIV activity.[122a,130] 5-(1-Adamantyl)-1,3,4-oxadiazoline-2-thione **249** was prepared from adamantane-1-carbohydrazide in 81% yield and was found to be the most active amongst the compounds tested for both antimicrobial and anti-HIV activity (Figure 44).

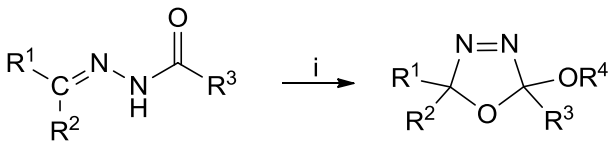


249

Figure 44: Δ^2-1,3,4-Oxadiazoline with biological activity

4.6 Δ^3-1,3,4-Oxadiazolines

As discussed in the review of 1,3,4-oxadiazolines by Hill, Warkentin *et al.* synthesised Δ^3-1,3,4-oxadiazolines **250** by the reaction of acylhydrazones **251** with lead tetraacetate in the appropriate alcohol (Scheme 95).[131] This reaction was carried out in neat ethanol or in dichloromethane and oxadiazoline yields ranged between 40-80%.

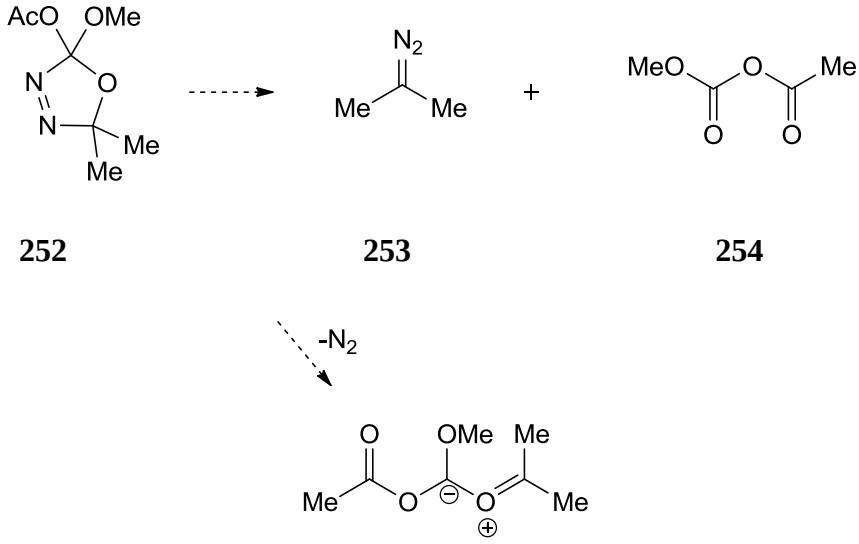


251 **250**

Scheme 95: Reagents: (i) $Pb(OAc)_4$, R^4OH[131]

4.7 Decomposition of oxadiazolines

Thermal cycloreversion of oxadiazolines has been investigated by Warkentin *et al.*, but the results are not as clear-cut as hoped.[132] The thermolysis of 2-acetoxy-3-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline **252** was investigated and it was found that two competing cycloreversion reactions were taking place (Scheme 96). The first of which (lowest energy cycloreversion) gave rise to 2-diazopropane **253** and a mixed anhydride **254**. Secondly, following the extrusion of nitrogen, evidence for a carbonyl ylide **255** was found in the form of acetone and methyl pyruvate. The methyl pyruvate was formed by rearrangement of the carbonyl ylide. A computational study [B3PW91/6-311+G(2df, p) level] was used to support the results and as a means of understanding more about the cycloreversion process.



252 **253** **254**

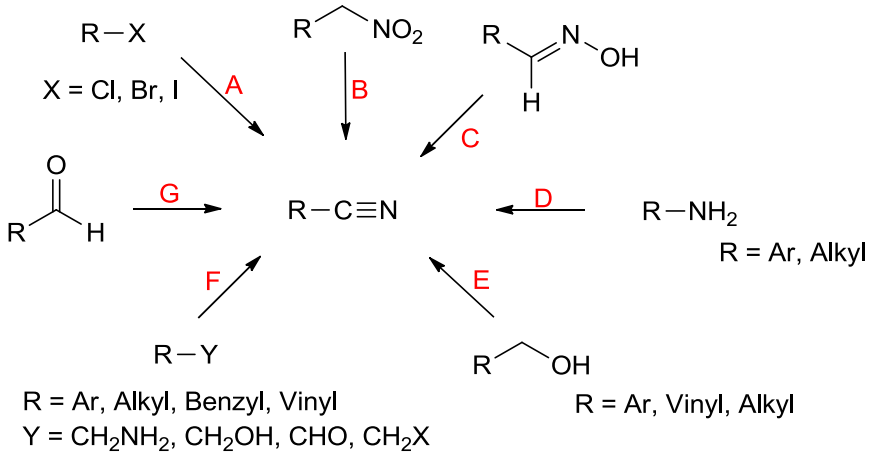
255

Scheme 96: Thermolysis of 252[132]

5 Synthesis of nitriles

Nitriles are described as compounds containing the cyano group (-C≡N). The most common route to nitriles is by the reaction of a cyanide salt with alkyl halides to generate a nitrile

group in the molecule (Method A in Scheme 97). This is a nucleophilic substitution reaction in which sodium or potassium cyanide are typically used. The cyanide ion can displace a variety of leaving groups, in this example, the halide ion. Another feature of this reaction is that it is a carbon-carbon bond forming reaction.



Scheme 97: Method A Reagents: (i) NaCN or KCN; Method B[43] Reagents: (i) 1.1 eq. BnBr, 1.05 eq. KOH, 5 mol% Bu_4NI, THF, r.t., 3 h: (ii) 4.5 eq. $SOCl_2$, 9 eq. NEt_3, -20 °C, 12 h. Method C[133] Reagents: (i) 1 eq. $MeSO_2Cl$, graphite (cat.), neat, 100 °C, 5-20 min. Method D[134] Reagents: (i) 0.6 eq. TCBDA, 3 eq. NEt_3, DMF, 25 °C, 1-2 h. Method E[135] Reagents: (i) 1.1 eq. NH_4HCO_3, 1 eq. $(Bu_4N)_2S_2O_8$, 3 mol% $Cu(HCO_2)_2.Ni(HCO_2)_2$, 1 eq. KOH, *i*PrOH/H_2O (1:1), 25 °C, 1.5-2 h. Method F[136] Reagents: (i) 0.75 eq. TCCA, aq. HN_3 (15M), 60 °C, 1-5 h. Method G[137] Reagents: (i) $NH_2OH.HCl$ (1.1 eq.), DMSO, 90 °C, 1-2 h

However, alkyl halides are not the only starting material which can be used in the synthesis of nitriles. Nitriles can be accessed from nitroalkanes, oximes, aldehydes, amines and alcohols (Routes B to E in Scheme 97).The conversion of oximes and primary nitroalkanes into nitriles is of particular relevance to the subject matter of this thesis (Chapter 2).

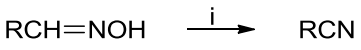
5.1 Nitriles from nitroalkanes (Method B)

Creedon developed new routes for the synthesis of nitriles and isonitriles.[138] Utilising the 1,3-dipolar cycloaddition reaction of a nitrile oxide (generated *in situ* from a nitroalkane) with a formamidine, followed by decomposition of the resulting Δ^2-1,2,4-oxadiazoline to a nitrile and urea, formed the basis of a novel route to nitriles from nitro compounds. This research was further explored by Levis who investigated the synthesis of nitriles from nitroalkanes *via* heterocyclic intermediates.[139] This body of work examined the possibility of developing a cascade reaction involving the decomposition of Δ^2-1,2,4-oxadiazolines, resulting in nitrile and urea products. Following on in this line of research, Hogan examined Δ^2-1,2,4-oxadiazolines as a route to nitriles *via* nitrile elimination from the heterocycle without isolation of the (reactive) heterocycle.[140]

5.2 Nitriles from aldoximes (Method C)

Shono *et al.* explored the transformation of aldoximes into nitriles *via* electrochemical means.[33]A number of aldoximes (**256a-d**) were examined with nitrile (**257a-d**) being isolated in appreciable yields (Table 4).

Table 4: Aldoximes which were examined by Shono *et al* in the preparation of nitriles

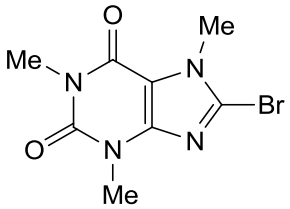


256a-d **257a-d**

Entry	Aldoxime	R	Charge (F/mol)	Nitrile	Yield (%)
1	**256a**	$CH_3(CH_2)_5$-	3.5	**257a**	83
2	**256b**	Cyclohexyl-	3.5	**257b**	71
3	**256c**	Ph-	4.5	**257c**	61
4	**256d**	2,4,6-$(CH_3)_3$Ph	5.0	**257d**	91

Acetic anhydride is the typical reagent of choice for the dehydration of oximes, however many other reagents such as acetyl chloride, thionyl chloride, ethyl chloroformate, phosphorous pentoxide, phenyl isocyanate and titanium tetrachloride have been used. [141]

More recently, Behrouz *et al.* investigated the use of 8-bromocaffeine **258** in the conversion of aldoximes into nitriles with the aim of establishing a mild, rapid and universally applicable method for nitrile synthesis (Figure 45).[142]



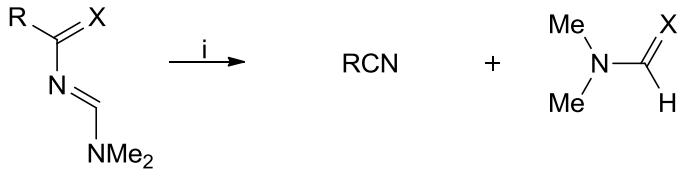
258

Figure 45: 8-Bromocaffeine 258

Conventional heating *versus* microwave-assisted conditions were explored with DBU as the base in DMF. Microwave-assisted reactions gave nitriles in yields of up to 96% (R = *p*-nitrophenyl) within 30 sec.

5.3 Nitriles from azapropenones

Mc Nab *et al.* investigated the pyrolysis of azapropenones **259** as a means of generating nitriles and amides (Scheme 98).[143] Azapropenones are thermally stable compounds when X = O, S. To overcome this stability effect, harsh reaction conditions (temperatures of 900 ^{o}C) must be employed. Extreme reaction conditions may account for the low yields of nitriles (20-35%) and amides or thioamides (7-30%) obtained.

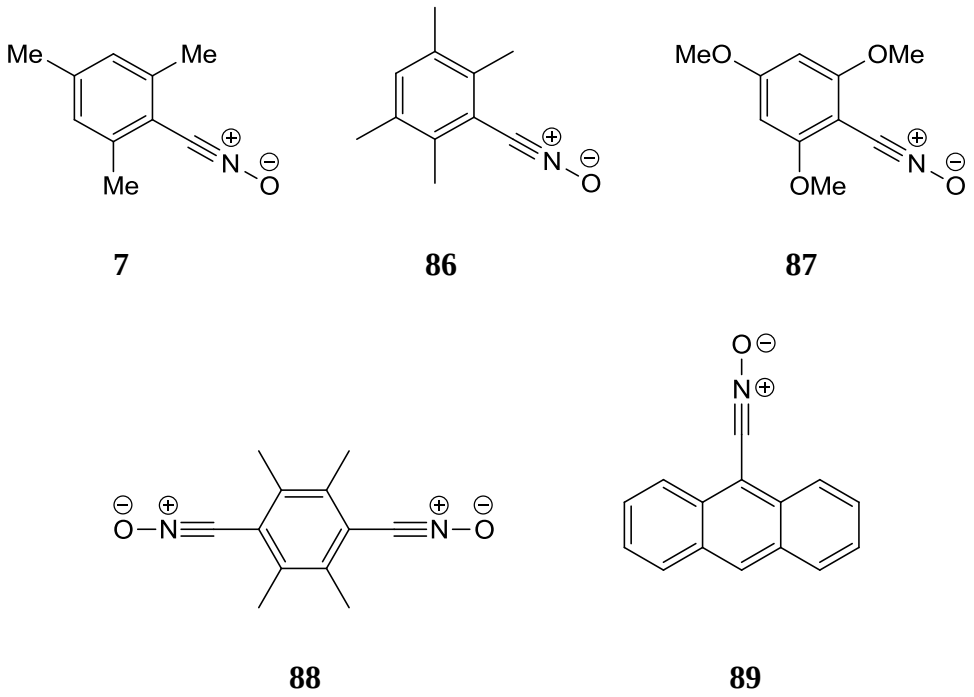


259a	X = S, R = Me	**260a, d**	R = Me	**261a-b**	X = S
259b	X = S, R = Ph	**260b, e**	R = Ph	**261c-f**	X = O
259c	X = O, R = H	**260c**	R = H		
259d	X = O, R = Me	**260f**	R = *p*-Tolyl		
259e	X = O, R = Ph				
259f	X = O, R = *p*-Tolyl				

Scheme 98: Reagents: (i) Heat

5.4 Nitriles from nitrile oxides[143]

While investigating the stability of nitrile oxides, Grundmann *et al.* discovered that reaction of the nitrile oxides with trimethylphosphite resulted in almost quantitative reduction of the nitrile oxides 2,4,6-trimethylbenzonitrile oxide **7**, 2,3,5,6-tetramethylbenzonitrile-*N*-oxide **86**, 2,4,6-trimethoxybenzonitrile-*N*-oxide **87**, tetramethylterephthalo-*bis*-nitrile-*N*-oxide **88** and anthracene-9-yl-nitrile-*N*-oxide **89** to their corresponding nitriles (Figure 46).[12d]



7 **86** **87**

88 **89**

Figure 46: Sterically hindered nitrile oxides

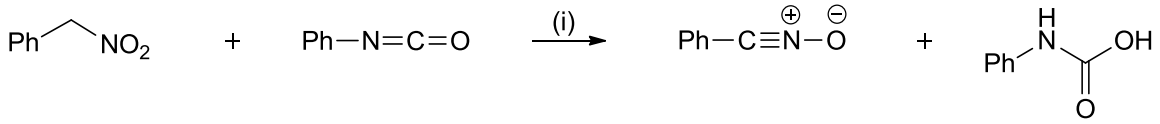
Methods for the synthesis of nitriles are important in view of the utility of these compounds in synthesis - they undergo or facilitate a wide range of useful functional group transformations. Issues relating to a novel process for the production of nitriles from heterocyclic precursors (1,2,4-oxadiazolines) and chemistry related to the generation of these heterocycles from nitrile oxide cycloadditions with imine derivatives (mostly amidines) will be addressed in the next chapter.

Chapter 2
Results and Discussion

The objective of our research was a study of the synthesis and reactivity of nitrile oxides as 1,3-dipoles in cycloaddition reactions with formamidines.

This objective was addressed through the synthesis of certain imines - mostly formamidines and investigations of their reactions with selected nitrile oxides generated *in situ* from their precursors e.g. hydroximoyl chlorides in the majority of cases.

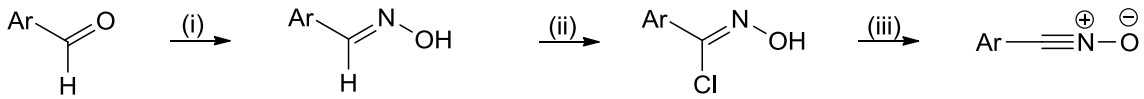
Earlier work by Levis explored two methods of generating nitrile oxides.[139] Firstly, they were generated *in situ* from primary nitroalkanes using the Mukaiyama procedure (Scheme 99).[39]



262 **263** **27** **264**

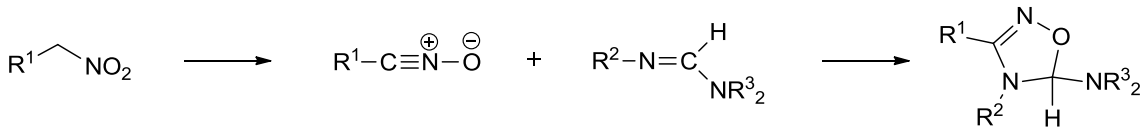
Scheme 99: Reagents: (i) NEt_3

The second process involved conversion of an aldehyde into its corresponding oxime, which in turn was halogenated and dehydrohalogenated to give a nitrile oxide *in situ* (Scheme 100).[144]



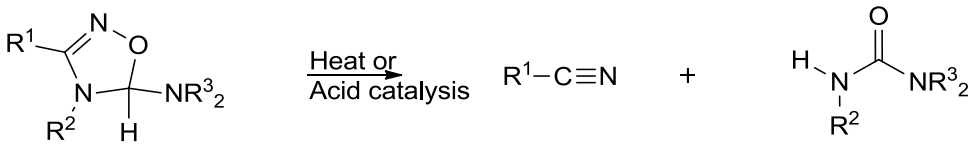
Scheme 100: Reagents: (i) $NH_2OH.HCl$, Base, solvent; (ii) $Cl_{2(g)}$ or NCS, chloroform; (iii) NEt_3

This earlier research work focused on development of a cascade in which production of a nitrile from a primary nitroalkane would be achieved through a heterocyclic intermediate (Scheme 101) which, without the addition of catalysts or other reagents generates the nitrile (Scheme 102). Nitriles are a valuable synthetic precursor in organic chemistry as they undergo or facilitate a wide range of useful functional group transformations.



Scheme 101: Conversion of a primary nitroalkane to a heterocyclic intermediate

From this study, it was apparent that nitrile oxides undergo rapid 1,3-dipolar cycloadditions with formamidines to give Δ^2-1,2,4-oxadiazolines. These heterocycles decompose upon heating or with acid catalysts, producing a nitrile and urea (Scheme 102).[139]

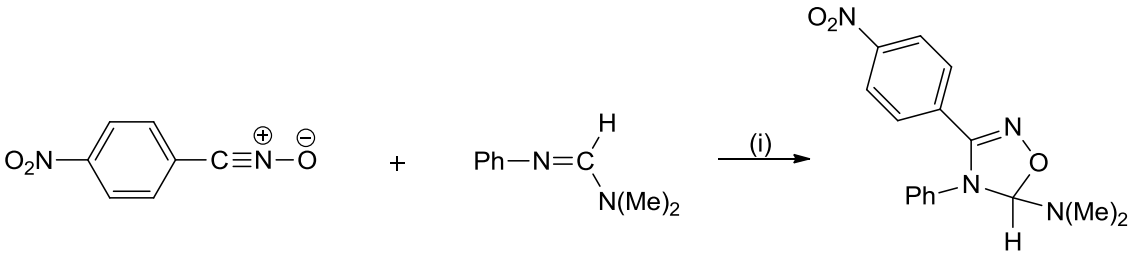


Scheme 102: Decomposition of Δ^2-1,2,4-oxadiazolines

It was anticipated that a reactive Δ^2-1,2,4-oxadiazoline would decompose rapidly to a nitrile and urea. It had been noted by Creedon that the rate of nitrile elimination could be accelerated by the presence of electron donating substituents at position -3 and -4 of the five-membered ring and the nitrogen substituent at position -5 of the heterocycle.[138] C. Levis hoped to develop a new synthetic procedure leading to a room temperature 'cascade based' process whereby the oxadiazoline intermediate would not be isolated or observed, thus developing a new mild and extremely efficient transformation of primary nitroalkanes into nitriles (Scheme 103).

Scheme 103: Proposed route to nitriles

Further to this work, another researcher Hogan investigated the isolation of a range of Δ^2-1,2,4-oxadiazolines.[140] This involved the reaction of a series of nitrile oxides with a selection of formamidines. The nitrile oxides chosen for this study contained electron-withdrawing substituents, a property which served to increase the stability of the Δ^2-1,2,4-oxadiazolines, i.e. they could be isolated and characterised as crystalline solids (Scheme 104).

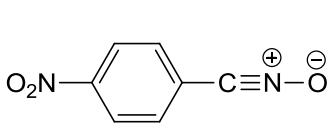


265 **266** **267**

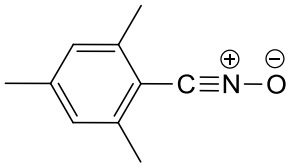
Scheme 104: Reagents: (i) Ether, room temperature

During that research it was observed, that nitrile oxides appeared to react rapidly with formamidines at room temperature to give Δ^2-1,2,4-oxadiazolines such was the case that the oxadiazolines were produced quantitatively within minutes of mixing the nitrile oxide precursor with a formamidine in the presence of a base. This raised the question: could the rates of these formamidine-nitrile oxide cycloadditions approach the limits of diffusion controlled processes? Diffusion controlled reactions would be considered to be novel in organic transformations as typically, reactions involving the formation of carbon-carbon and carbon-nitrogen bonds have significantly higher activation energies than e.g. electron and proton transfer reactions. As the formamidine is an electron rich dipolarophile, an inverse electron demand reaction mechanism may operate for the cycloaddition process whereby the HOMO-LUMO interaction in the transition state could be the opposite of that normally encountered for nitrile oxide cycloadditions (see chapter 1, 1,3-Dipolar Cycloadditions: orbital interactions).

Our current research work aims to explore reactivity in the 1,3-dipolar cycloaddition reaction of nitrile oxides with formamidines in the synthesis of Δ^2-1,2,4-oxadiazolines. The nitrile oxides chosen to initiate this study are well documented in the literature.[12i,12m,14a,b,14d-f,14h-j,23a,24d,31d,35,51a,65d,145] The majority are reactive molecules, generated *in situ* from a precursor. A few, however, e.g. *p*-nitrobenzonitrile oxide **265** and mesitonitrile-*N*-oxide **7** are stable, isolable species, in particular the latter which is stable owing to the substitution pattern of its aromatic ring (Figure 47). This property makes it suitable for NMR spectroscopy studies of cycloaddition reactions. The early sections of this chapter describe our work on the synthesis of nitrile oxide precursors, amidines and reference materials for reaction product identification.



265



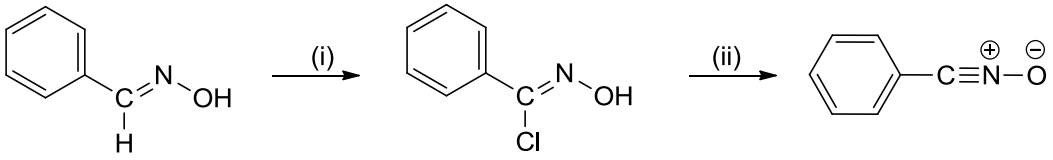
7

Figure 47: Nitrile oxides 265 and 7

1 Preparation of nitrile oxide precursors

1.1 The nitrile oxides

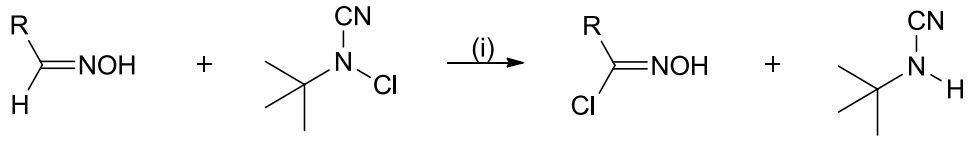
The preparation of nitrile oxides, either as reactive intermediates in solution or as isolable species has been addressed by numerous research groups.[22-23,26,28g,30,31c,32,37-38,45a,46-48,146] Many different procedures exist as outlined in chapter 1 of this thesis. The procedure for the synthesis of nitrile oxides was first described by Werner and Buss.[22] They generated benzonitrile oxide **27** by chlorination of benzaldoxime **25** to give benzohydroximoyl chloride **26**, followed by dehydrohalogenation with sodium carbonate (Scheme 105). This method is the most common route to nitrile oxides and the method we employed in our study. The oxime was synthesised from the aldehyde using the Fieser method and in all cases one isomer was isolated which was assumed to be the *E*-isomer.



25 **26** **27**

Scheme 105: Reagents: (i) $Cl_{2(g)}$, ether, r.t.; (ii) Sodium hydroxide, ether

Both hydroximoyl chlorides and bromides were investigated during the course of our research. A number of halogenating agents such as chlorine, thionyl chloride and oxalyl chloride were examined. The chlorination of the oximes *via* chlorine gas proved to be the more robust method. Kaushik *et al.* explored the use of *N*-tert-butyl-*N*-chlorocyanamide **268** as a chlorinating agent in the synthesis of hydroximoyl chlorides (Scheme 106).[25]



268 **269**

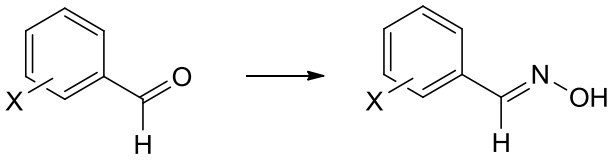
Scheme 106: Reagents: (i) DCM, r.t., <1 min

This novel chlorination method yielded the hydroximoyl chloride within a minute of stirring with the reagent **268** in dichloromethane at room temperature. It was reported that the hydroximoyl chloride was isolated in 'virtually quantitative yields' and no evidence of over chlorination or interference from other substituents was observed. The presence of electron

donating groups, electron withdrawing groups or an aromatic ring in the oxime molecular structure did not affect the yields/efficiency or the rate of reaction.

1.1.1 Synthesis of substituted benzohydroximoyl chlorides

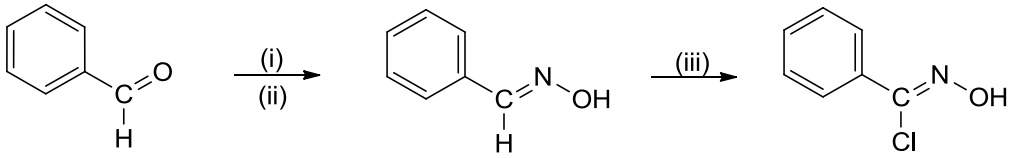
Benzaldoxime **25** was generated by the addition of sodium hydroxide to benzaldehyde, followed by hydroxylamine hydrochloride (Scheme 107).[144]



270	X = H	**25**	X = H
271	*p*-NO_2	**272**	*p*-NO_2
273	*m*-NO_2	**274**	*m*-NO_2

Scheme 107: Conversion of the aldehyde to the oxime

Carbon dioxide was then bubbled through the solution resulting in the precipitation of the oxime. Following an aqueous work-up and distillation at water aspirator pressure (b.p. 114-124°C @ 25 mmHg), the oxime **25** was isolated in 82% yield. Its boiling point and spectroscopic properties correlated with those reported in the literature for the compound.[140]



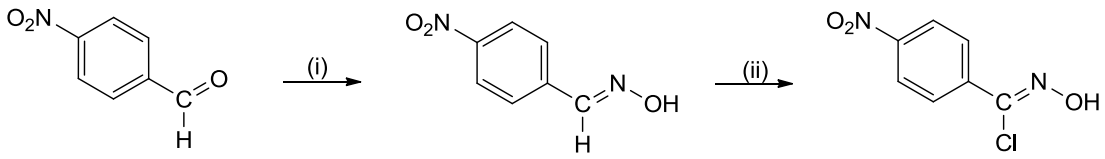
270 **25** **26**

Scheme 108: Reagents: (i) NaOH, $NH_2OH.HCl$, water; (ii) $CO_{2(g)}$; (iii) $Cl_{2(g)}$, chloroform, < -10°C

The subsequent step involved the reaction of the oxime **25** with chlorine gas to produce benzohydroximoyl chloride **26** (Scheme 108). The progress of this reaction is accompanied by colour change.[147] This was outlined by Gilchrist as involving transient 'vinyl nitroso compounds' in solution which 'have been detected spectroscopically or simply by the appearance of a characteristic blue colour in the solution'.[148] On saturation with chlorine, the reaction mixture turned a dark orange colour. The product **26** was isolated as a pale cream solid in 43% yield following recrystallisation from cold hexane. Its melting point (51°C) and spectroscopic properties were consistent with those reported in the literature.[140]

1.1.1.1 *p*-Nitrobenzohydroximoyl chloride

p-Nitrobenzaldoxime **272** was produced by heating a mixture of *p*-nitrobenzaldehyde, hydroxylamine hydrochloride and sodium acetate to reflux in 95% ethanol for 28 h (Scheme 109). The oxime **272** was isolated as a pale yellow crystalline solid in 78% yield following recrystallisation from ethanol/water. Its melting point (130-132°C) and spectroscopic properties correlate to those reported in literature for the *E*-isomer.[149]



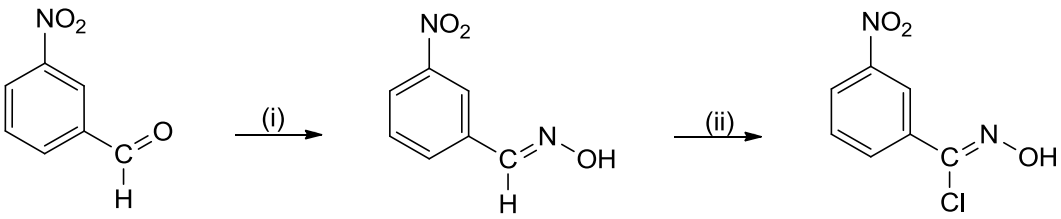
271 **272** **275**

Scheme 109: Reagents: (i) NaOAc, $NH_2OH.HCl$, ethanol, reflux 28 h; (ii) $Cl_{2(g)}$, chloroform, <0°C

The subsequent step again involved the reaction of the oxime **272** with chlorine gas to generate *p*-nitrobenzohydroximoyl chloride **275**. The progress of this reaction was monitored by colour change. Upon saturation with chlorine the reaction solution turned a deep yellow/orange colour. The product **275** was isolated as a pale yellow crystalline solid in 58% yield following recrystallisation from cold chloroform/hexane. Its melting point (124-125°C) correlated with the literature value (123-124°C).[145b] Its spectroscopic properties (NMR and IR) were consistent with the molecular structure involved and agreed with those reported in the literature.

1.1.1.2 *m*-Nitrobenzohydroximoyl chloride

m-Nitrobenzaldoxime **274** was similarly prepared from *m*-nitrobenzaldehyde, hydroxylamine hydrochloride and sodium acetate in ethanol (Scheme 110). The oxime **274** was isolated as a pale yellow crystalline solid in 95% yield. Its melting point (115-119°C) and spectroscopic properties were consistent with those reported in the literature.[14d,150]



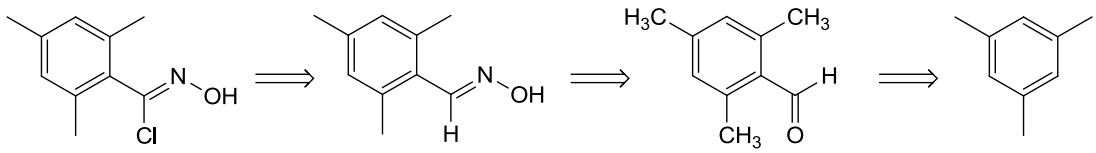
273 **274** **276**

Scheme 110: Reagents: (i) NaOAc, $NH_2OH.HCl$, ethanol, reflux 28 h; (ii) $Cl_{2(g)}$, chloroform, < 0°C

The chlorination step involved the reaction of the oxime **274** with chlorine gas to generate *m*-nitrobenzohydroximoyl chloride **276** (Scheme 110). The progress of this reaction was monitored by the usual colour change. On saturation with chlorine the solution turned a deep yellow colour. The product **276** was isolated as a yellow crystalline solid in a 61% yield following recrystallisation from cold chloroform/hexane. Its melting point (97-99^{o}C) and spectroscopic results correlate with those reported in the literature for *m*-nitrobenzohydroximoyl chloride **276**.[145b]

1.1.1.3 2,4,6-Trimethylbenzohydroximoyl chloride

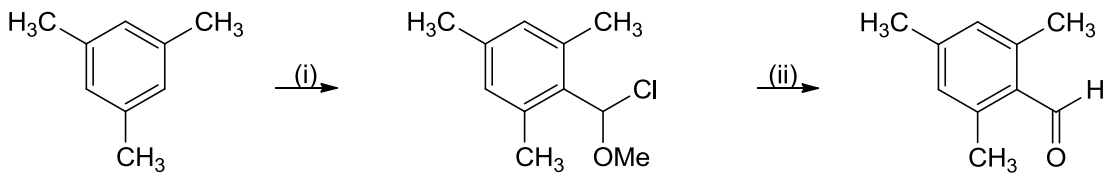
Synthesis of 2,4,6-trimethylbenzohydroximoyl chloride from mesitylene **277** involved three sequential steps. Firstly, the acylation of mesitylene *via* the mesitylene methyl ether intermediate **278** in the formation of mesitaldehyde **279**, secondly, the condensation of mesitaldehyde to form mesitaldoxime **280**, and finally, the synthesis of 2,4,6-trimethylbenzohydroximoyl chloride **281** (Figure 48).



281 **280** **279** **277**

Figure 48: Retrosynthetic analysis of 281

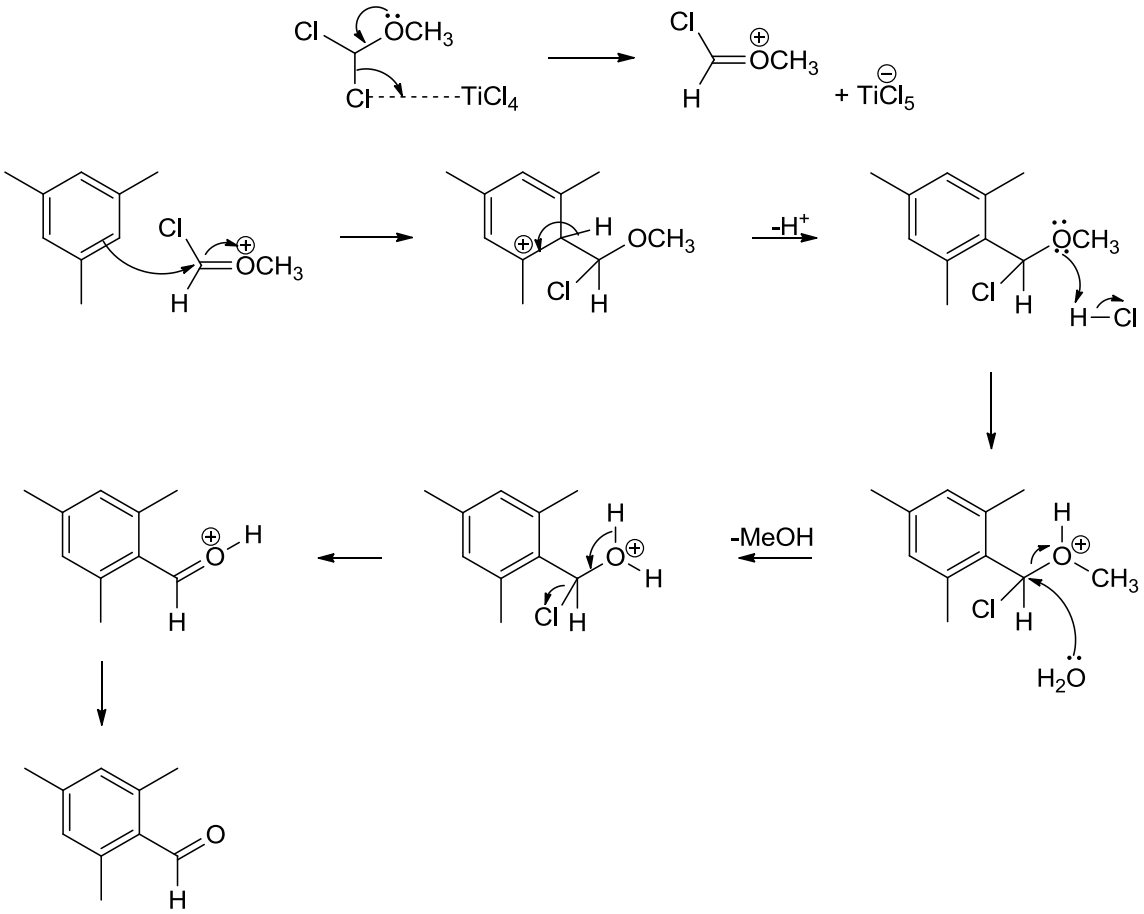
Mesitaldehyde **279** was prepared by the dropwise additions of titanium tetrachloride and then dichloromethyl methyl ether to mesitylene followed by gentle heating (35-40^{o}C) of the mixture to reflux for 15 min (Scheme 111). Following purification of the crude product by distillation at water aspirator pressure (102-112^{o}C @ 15 mmHg), mesitaldehyde **279** was isolated in 74% yield as a pale yellow oil. The boiling point correlates to that reported in the literature.[145c] The spectroscopic properties also agree with those reported in the literature.[151] The formyl proton signal was observed at δ_H 10.54 and the signal of the corresponding attached carbon of the aldehyde occurred at δ_C 193.4 ppm.



277 **278** **279**

Scheme 111: Reagents: (i) $TiCl_4$, $(Cl)_2CHOMe$, DCM, (ii) HCl, water

The proposed reaction mechanism for the formation of mesitaldehyde is outlined in Scheme 112.



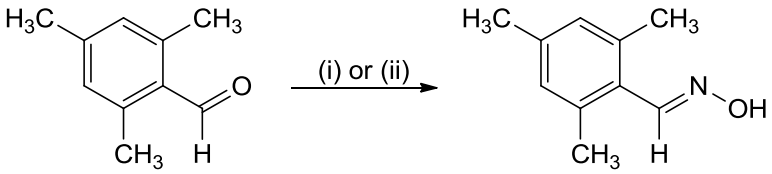
279

Scheme 112: The proposed mechanism for the formation of mesitaldehyde 279

Two different methods were employed synthesising mesitaldoxime **280**. Initially, following Liu *et al.*, the oxime **280** was prepared by adding 50% NaOH (aq.) solution to a stirring solution of hydroxylamine hydrochloride in mesitaldehyde **279** (Scheme 113, Method (i)).[14d] The solution was then stirred overnight. The solution of the oxime anion was acidified with conc. hydrochloric acid and the oxime was isolated following an aqueous work-up. The oxime

from this process was a pale yellow crystalline solid, isolated in 45% yield following recrystallisation from ethyl acetate/hexane. Its melting point (119-123°C) was in agreement with that reported in the literature.[24d] Its spectroscopic properties correlate with those reported in the literature.

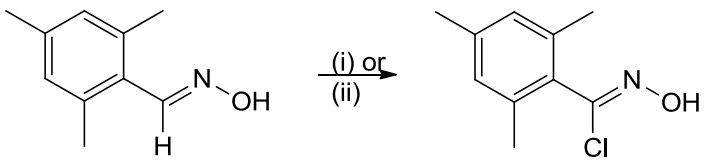
Secondly, mesitaldoxime **280** was prepared by the heating a mixture of mesitaldehyde, hydroxylamine hydrochloride and sodium acetate to reflux in ethanol for 24 h (Scheme 113, Method (ii)). The oxime **280** was isolated as a white crystalline solid in 65% yield following recrystallisation from ethanol/water. Its melting point (119-121°C) was slightly lower, but its spectroscopic properties correlate with those reported in the literature and are identical to method 1.[24d]



279 **280**

Scheme 113: Reagents: (i) $NH_2OH.HCl$, NaOH, or (ii) $NH_2OH.HCl$, NaOAc, ethanol

Two methods were employed in the synthesis of 2,4,6-trimethylbenzohydroximoyl chloride **281.** The first involved adding *N*-chlorosuccinimide to a stirring solution of mesitaldoxime **280** in DMF (Scheme 114). This was carried out in the presence of HCl gas to help initiate the chlorination reaction. The benzohydroximoyl chloride **281** was isolated as a white solid in 97% yield. Its melting point (66-74.5°C) is within the range of the literature data for the compound and the spectroscopic properties, IR and ^{1}H NMR spectroscopy, agree with those reported in the literature and with the structure itself.[12d,24d]



280 **281**

Scheme 114: Reagents: (i) NCS, $HCl_{(g)}$, DMF; (ii) Pyridine, Chlorofrom, r.t., NCS

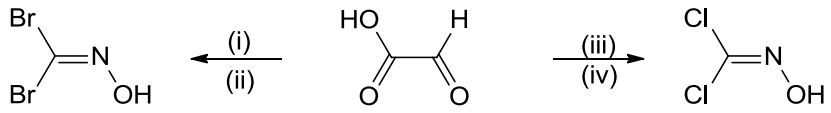
The second method employed was that outlined by Bode *et al.*, which involved adding pyridine to a stirring solution of the oxime in chloroform.[152] The solution was then heated to

40°C and NCS added. The chlorination was complete within 3 h and following an aqueous work-up, the hydroximoyl chloride **281** was isolated as a pale yellow solid in 91% yield. Its melting point (59-65°C) was within the range of the crude literature value outlined by Liu *et al*., however it lies outside the range of the purified value.[12d,14d] This may be attributed to isolation of the oxime as a mixture of both *syn*- and *anti*-isomers, however the spectroscopic data correlated well with the literature and suggested that only one isomer had been isolated.

1.1.2 Synthesis of dihaloformaldoximes

1.1.2.1 Dibromoformaldoxime

Dibromoformaldoxime **41** was generated by adding solid hydroxylamine hydrochloride to a stirring solution of glyoxylic acid monohydrate **282** (Scheme 115). Sodium carbonate was then added to the solution which resulted after stirring the mixture overnight. Dichloromethane was added as a surfactant and the solution was cooled prior to bromine addition. The reaction mixture was stirred overnight and an aqueous work-up yielded the oxime as a white crystalline solid in 44% yield. Its m.p. (55.5-60°C) and carbon-13 NMR spectroscopic resonance at 99.2 ppm correlated with the literature.[35]

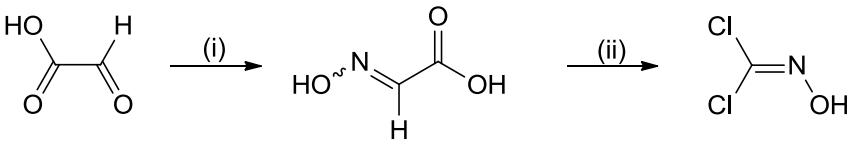


41 **282** **16**

Scheme 115: Reagents: (i) $NH_2OH.HCl$, water, r.t., (ii) $NaHCO_3$, DCM, cooled to 0°C, Br_2; (iii) a) $NH_2OH.HCl$, b) 1M $NaOH_{(aq)}$, c) 2M H_2SO_4, d) Extraction with ether., (iv) NCS, chloroform, reflux

1.1.2.2 Dichloroformaldoxime

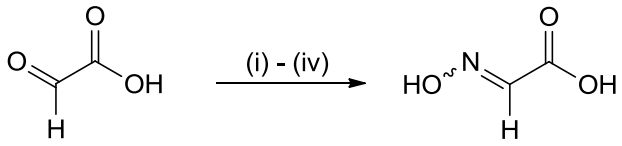
The two-step synthesis employed involved the preparation of glyoxylic acid aldoxime **283** first. Dichloroformaldoxime **16** was then formed from the decarboxylative halogenation of glyoxylic acid aldoxime (Scheme 116).



282 **283** **16**

Scheme 116: Reagents: (i) a) $NH_2OH.HCl$, b) 1M $NaOH_{(aq)}$, c) 2M H_2SO_4, d) extraction with ether.; (ii) NCS, chloroform, reflux

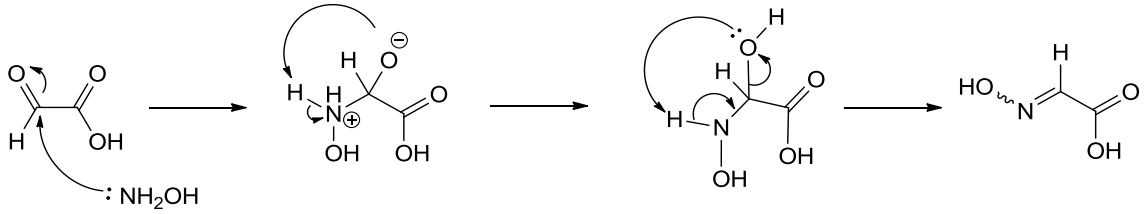
Glyoxylic acid aldoxime **283** was the selected precursor of dichloroformaldoxime **16** (Scheme 117). It was initially produced by heating glyoxylic acid monohydrate with hydroxylamine hydrochloride to reflux. However, the yield was extremely low at 3%.



282 **283**

Scheme 117: Reagents: (i) $NH_2OH.HCl$, (ii) 1M $NaOH_{(aq)}$, (iii) 2M H_2SO_4, (iv) extraction with ether

An alternative method was adapted from the procedure outlined by Wieland in 1910.[153] The first attempt at this procedure involved stirring glyoxylic acid with hydroxylamine hydrochloride in water, basifying the solution and stirring overnight. The solution was acidified with sulphuric acid and the product extracted into ether. This gave the oxime in 5% yield with spectroscopic properties that correlate well with the structure. The proposed reaction mechanism is outlined in Scheme 118.



282 **283**

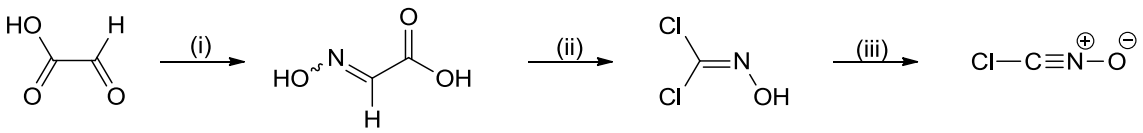
Scheme 118: The proposed reaction mechanism

A slight modification to the Wieland procedure, by concentrating the reaction mixture prior to the extraction into ether, gave the oxime in 78% yield. Its melting point is more indicative of a salt (>304^{o}C). However, carbon-13 NMR spectroscopic data is consistent with the molecular structure (Table 5). As there is no acidification in this method, it is more likely that the isolated material is the sodium salt of glyoxylic acid aldoxime.

Table 5: The ^{13}C NMR spectroscopic data of glyoxylic acid aldoxime 283

$\delta_{C(ppm)}$	
CH=NOH	143.1
COOH	165.9

Dichloroformaldoxime **16** was generated following the procedure outlined by Torssell *et al.* by the decarboxylative halogenation of glyoxylic acid aldoxime **283** with *N*-chlorosuccinimide (Scheme 119).[145i] The chloro-oxime **16** was isolated and used directly in the generation of the nitrile oxide **17** without further analysis or purification.



282 **283** **16** **17**

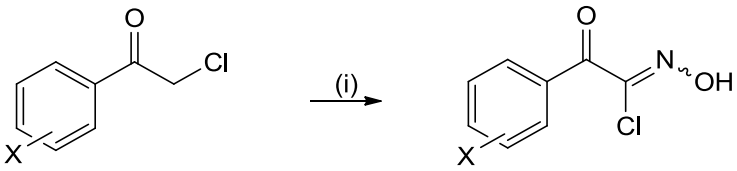
Scheme 119: Reagents: (i) a) $NH_2OH.HCl$, b) 1M $NaOH_{(aq)}$, c) 2M H_2SO_4, d) extraction with ether.; (ii) NCS, chloroform, reflux; (iii) NEt_3, ether, 0°C

1.1.3 Synthesis of 1-aroyl-1-chloroformaldoximes

1.1.3.1 1-Benzoyl-1-chloroformaldoxime

Kozhevnikov *et al.* discussed the preparation of 1-benzoyl-1-chloroformaldoxime **286** from its corresponding ketone **285** using *iso*-propyl nitrite, as did Levin *et al*. and also Brachwitz.[154] Alternative syntheses include the nitrosation of *β*-keto sulfoxides, treatment of *α*-haloketones with alkyl thionitrites under mild conditions.[12f,155] For the most part, the alkyl thionitrite route was regarded as a better alternative to the nitrosation route due, '*both to the more facile cleavage of sulphur-nitrogen bond than that of oxygen - nitrogen bond of nitrites and also to the better leaving group of the thiolate (RS ⁻) moiety than alkoxy (RO ⁻) in the nitrosation step*'.

Tegeler *et al.* outlined a procedure for the synthesis of 1-benzoyl-1-chloroformaldoxime **286** and some substituted versions using butyl nitrite as a reagent (Scheme 120).[65d]

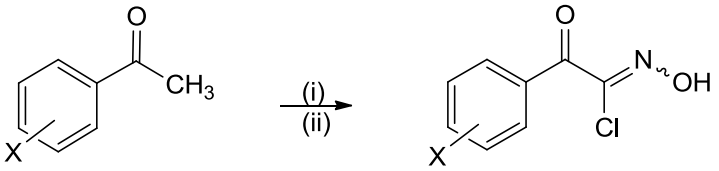


284 X = H
287 X = CH_3
289 X = CH_3O

286 X = H
288 X = CH_3
290 X = CH_3O

Scheme 120: Reagents: (i) Butyl nitrite, $HCl_{(g)}$

However, *iso*-propyl nitrite and butyl nitrite are known heart stimulants and we were reluctant to use them from a health and safety point of view.[156] This brought us to the Šunjić *et al.* procedure which uses reagents that are potentially less harmful (Scheme 121).[145d]



285 X = H **286** X = H
291 X = *p*-Br **292** X = *p*-Br

Scheme 121: Reagents: (i) 15% aq. HCl/ $NaNO_2$, (ii) HNO_3, 70°C

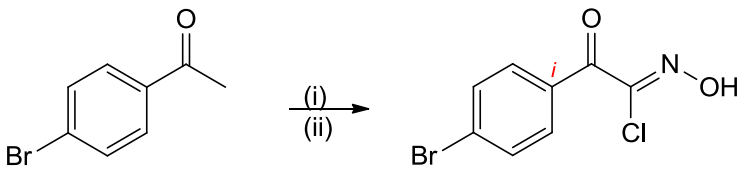
1-Benzoyl-1-chloroformaldoxime **286** was successfully synthesised from acetophenone **285** by the Šunjić method (Scheme 121).[145d] The chloro-oxime **286** was isolated by extraction with dichloromethane affording the title compound as a yellow solid in 77% yield. Its melting point (128-131°C) shows good correlation with the literature value (130-131°C) as does the NMR spectroscopic analysis (Table 6). The compound was isolated as one isomer, assumed to be the *E*-form.

Table 6: The ^{1}H and ^{13}C NMR spectroscopic data of 286

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
***m*-ArH**	7.47	**3 x ArCH**	128.4, 130.7 and 133.8
***p*-ArH**	7.62	***i*-ArC-**	134.8
***o*-ArH**	7.97	**-C(Cl)=NOH**	139.2
-OH	9.21	**-C=O**	183.9

1.1.3.2 1-(*p*-Bromobenzoyl)-1-chloroformaldoxime

1-(*p*-Bromobenzoyl)-1-chloroformaldoxime **292** is another example of an *α*-oximino-*α*-haloketone which was produced by modification of the procedure described by Šunjić *et al.* (Scheme 122).[145d] *p*-Bromoacetophenone **291** (rather than acetophenone) was treated with hydrochloric acid, sodium nitrite and nitric acid to yield 1-(*p*-bromobenzoyl)-1-chloroformaldoxime **292** as a pale yellow solid in 17% yield, as a single isomer.



291 **292**

Scheme 122: Reagents: (i) 15% aq. HCl/ $NaNO_2$, (ii) HNO_3, 70°C

The purity of the compound was confirmed by elemental micro analysis which was within ±0.3% of the theoretical values. The ^{1}H and ^{13}C NMR spectroscopy resonances of **292** are detailed in Table 7.

Table 7: The ^{1}H and ^{13}C NMR spectroscopic data of 292

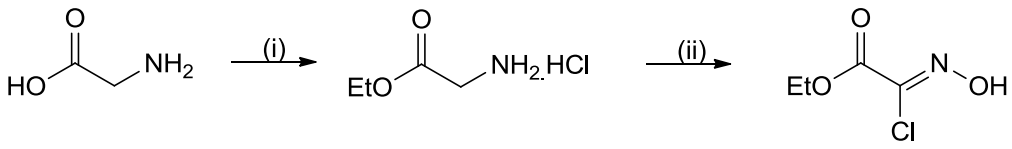
$\delta_{H\ (ppm)}$		$\delta_{C\ (ppm)}$	
Ar<u>H</u>	7.62	**Ar<u>C</u>(Br)**	129.27
Ar<u>H</u>	7.88	**Ar<u>C</u>H x 2**	131.74 and 132.12
-O<u>H</u>	8.83	***ipso* <u>C</u> of Ar**	133.42
		<u>C</u>(Cl)=NOH	139.40
		<u>C</u>=O	182.60

1.1.4 Synthesis of other hydroximoyl halides

1.1.4.1 Ethylchloroglyoxalate oxime

This two-step synthesis was initiated with the preparation of glycine ethyl ester hydrochloride **294** from glycine **293** (Scheme 123). The product then underwent nitrosation under acidic conditions to give the target molecule **295**.

Glycine ethyl ester hydrochloride **294** was prepared by bubbling HCl gas through a stirring solution of glycine in ethanol, followed by heating the solution to reflux for 19 h (Scheme 123). The hydrochloride salt **294** was isolated as a white solid (and used without further purification) in 94% yield. Its melting point (120-122^{o}C) was lower than that reported in the literature (144°C), but its spectroscopic properties agreed with the structure.[24a]

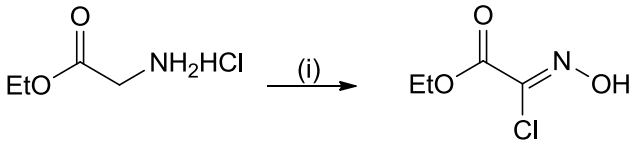


293 **294** **295**

Scheme 123: Reagents: (i) $HCl_{(g)}$, ethanol; (ii) HCl, $NaNO_2$

Ethylchloroglyoxalate oxime **295** was prepared by adding hydrochloric acid and sodium nitrite in alternate portions, followed by stirring the solution for 69 h (Scheme 124). The hydroximoyl chloride **295** was isolated in 24% yield as a colourless crystalline solid following recrystallisation from chloroform/hexane. Its melting point (80-81^{o}C) and spectroscopic properties correlate to those reported in the literature.[157] The absence of the

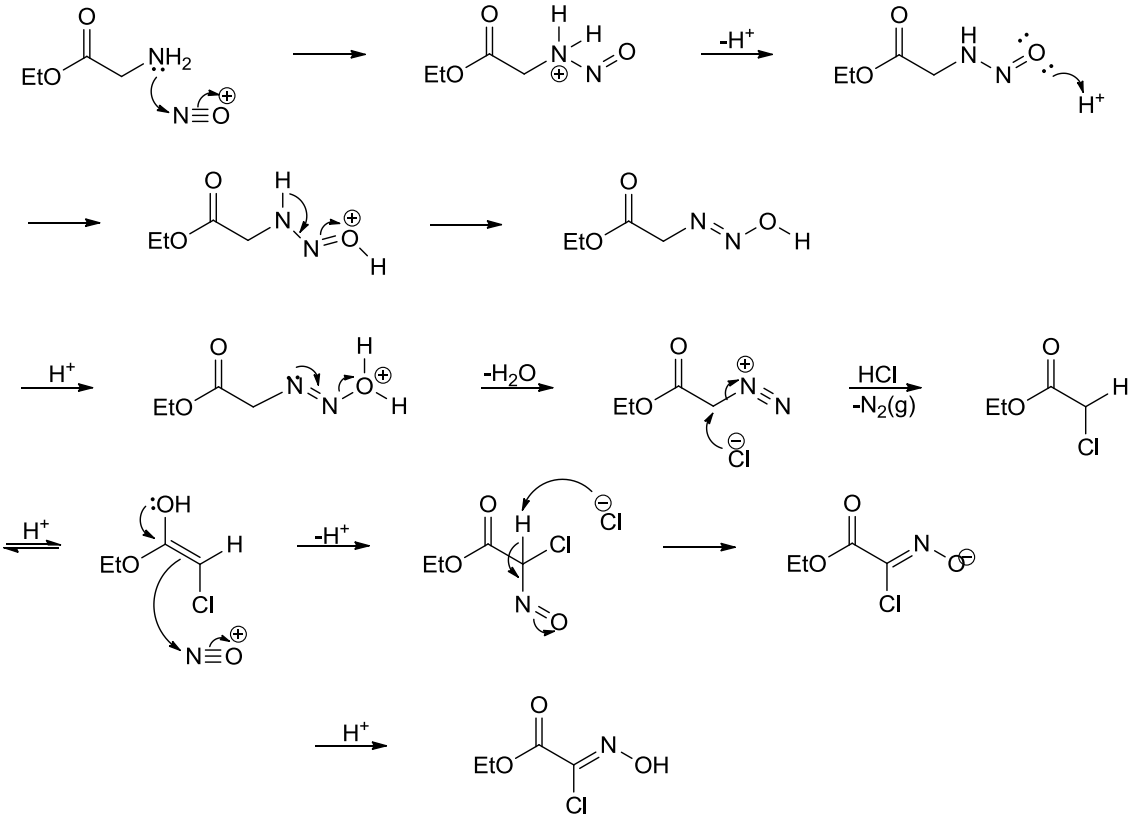
proton NMR resonance for the CH_2 group of glycine ethyl ester hydrochloride **294** at 3.81 ppm in the spectrum for **295** clearly indicates all **294** had been consumed in the conversion.



294 **295**

Scheme 124: Reagents: (i) HCl, $NaNO_2$

We propose the reaction mechanism as per Scheme 125.



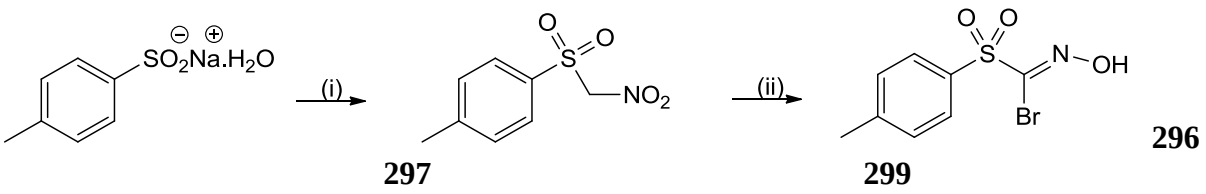
295

Scheme 125: Formation of ethylchloroglyoxalate oxime 295 from oxime 294

Ethylchloroglyoxalate oxime **295** has been shown to possess weak mutagenicity for *S. typhimurium* TA-100 and for mammalian V79 cells by Mirvish *et al.*.[158] We have encountered difficulties in handling this oxime **295** as it has caused skin blisters similar to those reported in the literature.[15]

1.1.4.2 1-*p*-Toluenesulfonyl-1-bromoformaldoxime

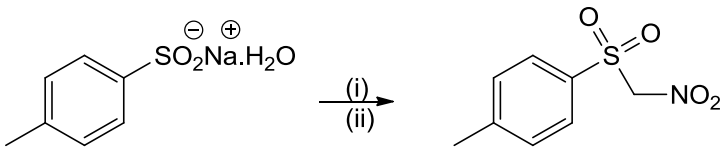
The synthesis of *p*-toluenesulfonylnitromethane **297** was followed by the production of diazomethane **298** (Scheme 126). The combination of these gave the simplest route to 1-*p*-toluenesulfonyl-1-bromoformaldoxime **299**.



297 **299** **296**

Scheme 126: Reagents: (i) a) NaOMe, CH_2NO_2, b) I_2, Na_2SO_3; (ii) a) NaOAc, DCM; b) Br_2, DCM, water; c) CH_2N_2(298)/ether; d) Reflux 15 min

p-Toluenesulfonylnitromethane **297** was prepared by adapting the procedure of Wade *et al.* for the corresponding conversion of sodium benzenesulfinate into benzenesulfonyl nitromethane (Scheme 127).[159]



296 **297**

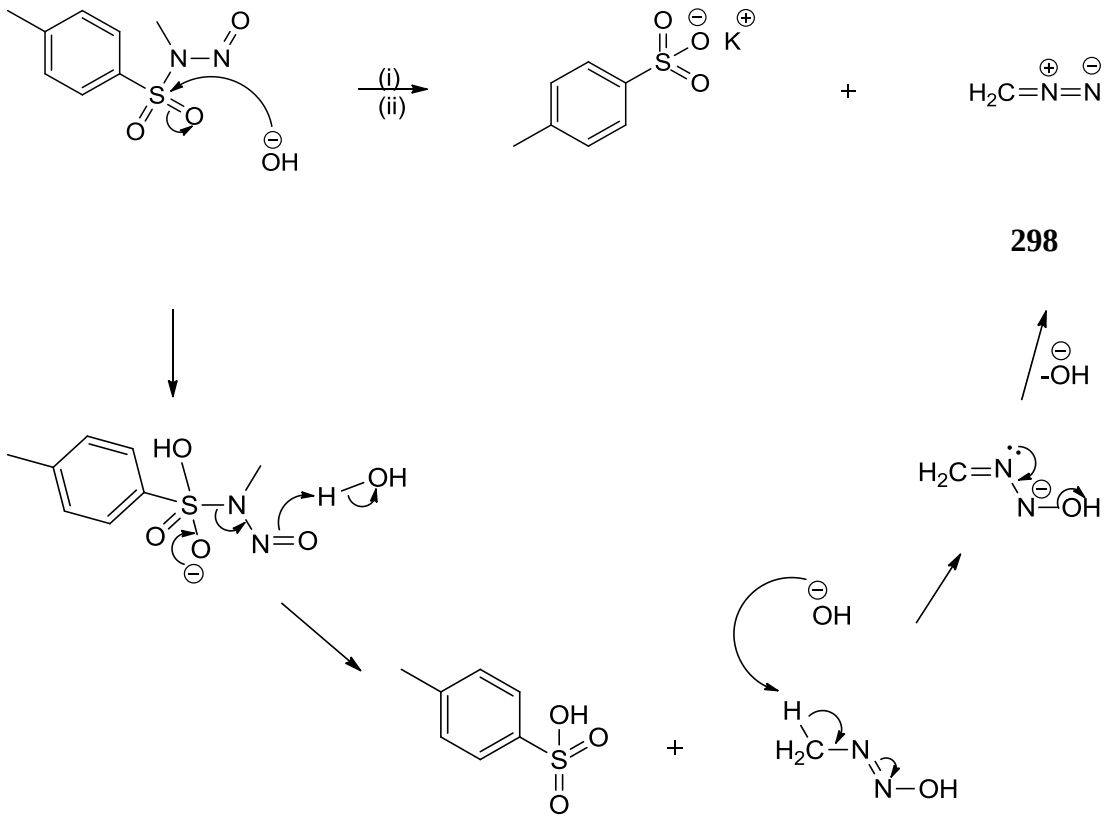
Scheme 127: Reagents: (i) NaOMe, CH_2NO_2, (ii) I_2, Na_2SO_3

The target compound **297** was isolated in 40% yield as a pink/orange solid. Its m.p. (115-116°C) was in agreement with the literature value (116°C).[160] Its spectroscopic properties reflect all components of the compounds molecular structure (Table 8).

Table 8: The ^{1}H and ^{13}C NMR spectroscopic data of 297

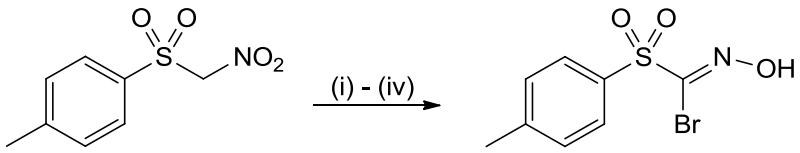
$\delta_{H(ppm)}$		**$\delta_{C(ppm)}$**	
Ar$C\underline{H}_3$	2.50	**ArC($\underline{C}H_3$)**	21.9
$C\underline{H}_2NO_2$	5.57	**$\underline{C}H_2NO_2$**	90.4
***o*-Ar$\underline{H}$ to SO_2**	7.44	***i*-Ar$\underline{C}$H**	147.2
***m*-Ar$\underline{H}$ to SO_2**	7.84	**2 x Ar$\underline{C}$H**	128.4 and 130.4
-		***p*-Ar$\underline{C}$(CH_3)**	132.6

Diazomethane **298** was generated from Diazald® following the procedure outlined by O' Leary[161] and used directly as an ethereal solution in the synthesis of **299** (Scheme 128).



Scheme 128: Reagents: (i) KOH, (ii) Reflux/distillation

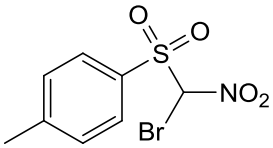
1-*p*-Toluenesulfonyl-1-bromoformaldoxime **299** was generated by adapting the procedure of Wade *et al.*[51b] (Scheme 129): *p*-Toluenesulfonylnitromethane **297** was used in place of phenylsulfonylnitromethane.



297 **299**

Scheme 129: Reagents: (i) NaOAc, DCM; (ii) Br_2, DCM, water; (iii) CH_2N_2/ether; (iv) Reflux 15 min

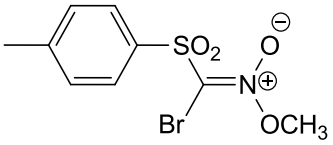
Following the bromine addition, the *mono*-brominated product **300** was identified by proton NMR spectroscopic analysis of the reaction product mixture(Figure 49).



300

Figure 49: The *mono*-brominated product of *p*-toluenesulfonylnitromethane 297

It is anticipated that the sequential bromination and *O*-methylation of the *α*–nitrosulfone **297** affords an unstable nitronic ester **301** which rapidly converts into the bromo oxime **299** (Figure 50).



301

Figure 50: The unstable nitronic ester intermediate

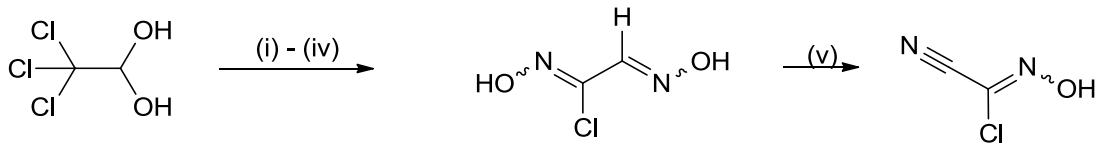
The bromooxime **299**, a known compound, was successfully isolated as a yellow solid in 77% yield following recrystallisation from dichloromethane:hexane.[18b] Its spectroscopic data agreed well with the structure of the bromooxime, but there is a lack of data in the literature for comparison purposes (see Table 9).

Table 9: The ^{1}H and ^{13}C NMR spectroscopic data of 299

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
Ar$C\underline{H}_3$	2.48	**Ar$C(\underline{C}H_3)$**	21.8
***o*-Ar$\underline{H}$**	7.40	***i*-Ar$\underline{C}$**	132.6
***m*-Ar$\underline{H}$**	7.89	***o*- & *m*-Ar$\underline{C}$H**	129.7 & 130.3
-O$\underline{H}$	9.47	***p*-Ar$\underline{C}(CH_3)$**	132.4
-		**$\underline{C}$=N**	146.6

1.1.4.3 Cyanoformohydroximoyl chloride

The synthesis of cyanoformohydroximoyl chloride **304** involved a number of steps. Intially, chloroglyoxime **303** was synthesised, followed by its dehydration to form cyanoformohydroximoyl chloride **304** (Scheme 130).



302 **303** **304**

Scheme 130: Reagents: (i) $NH_2OH.HCl$, K_2CO_3/H_2O, r.t.; (ii) 25% NaOH (aq) 0-5°C; (iii) 25%H_2SO_4 (aq); (iv) MTBE; (v) $SOCl_2$, ether

The synthesis of chloroglyoxime **303** proved to be more troublesome than previously anticipated. In all, four methods were investigated with three of these an attempt to synthesise chloroglyoxime as a one-pot synthesis. We found that a scaled down version of a procedure outlined by Burgoon *et al.* was the most reliable of these methods.[162]

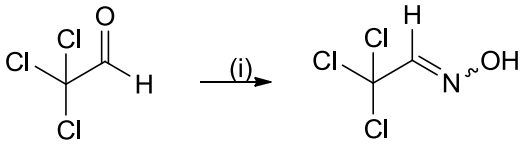
Chloroglyoxime was produced in 20% yield from chloral hydrate **302** and isolated as a white solid. Its melting point (154°C) was in good correlation with the literature.[163] Spectroscopic, proton and carbon NMR data (Table 10), confirm the structure of the compound **303**.

Table 10: The ^1H and ^{13}C NMR spectroscopic data of 303

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
-C<u>H</u>=N-	8.33	**-<u>C</u>H=N**	137.2
-O<u>H</u>	12.31	**N=<u>C</u>(Cl)**	142.5
-O<u>H</u>	12.52	-	

1.1.4.3.1 Synthesis of chloral oxime

One alternative route involved the preparation of chloral oxime **305** first, as it was the obvious precursor, which in turn was used as a reagent in the second step of the two-step synthesis of chloroglyoxime **303** (Scheme 131). Chloral oxime **305** was prepared utilising a modification of a method outlined by Tiemann *et al.*.[164] Anhydrous chloral **306**, hydroxylamine hydrochloride and calcium chloride were combined in water and stirred together firstly at room temperature, then at 50°C for 1 h. Distillation at water aspirator pressure afforded the *oxime* in 96% yield.



306 **305**

Scheme 131: Reagents: (i) $NH_2OH.HCl$, $CaCl_2$, H_2O

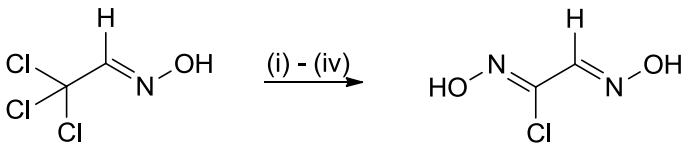
There is a dearth of data for compound **305** in the scientific literature with the boiling point as the only means to correlate data. The proton NMR spectrum clearly identified the hydrogens attached to the carbon of the oxime and the –OH group. Coupled to this information is the carbon spectrum which accounts for both carbons in the molecule (Table 11).

Table 11: The ^{1}H and ^{13}C NMR spectroscopic data of 305

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
-C<u>H</u>=N-	7.82	**-<u>C</u>H=N**	103.4
-O<u>H</u>	9.05	**-<u>C</u>(Cl)$_3$**	149.8

The procedure that we used was not in full conformity with that outlined in the literature.[164] The absence of an aqueous work-up, accounts for other products being present in the reaction mixture. Tiemann *et al.* distilled off any excess chloral following the aqueous work-up. Therefore, the additional peaks observed in the NMR spectrum implied that some of the reaction product was contaminated with chloral. There was a discrepancy in the boiling point of the reaction mixture (b.p. 41-44.5°C @20mmHg) when compared to the literature value (b.p. 82-83°C@14mmHg). The omission of the aqueous work up may account for this.

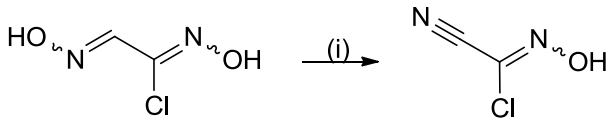
Chloral oxime **305** was then used as an intermediate in the preparation of chloroglyoxime **303** (Scheme 132). This method involved heating chloral oxime, hydroxylamine hydrochloride and sodium acetate to reflux in ethanol for 26h. However, this method yielded an unidentifiable product and the earlier route to chloroglyoxime **303** was examined.



305 **303**

Scheme 132: Reagents: (i) $NH_2OH.HCl$, NaOAc, 95% ethanol, 26 h reflux; (ii) 2M NaOH, H_2O; (iii) pH3 with glacial acetic acid; (iv) ether

Cyanoformohydroximoyl chloride **304** was synthesised following the procedure outlined by Kozikowski *et al*. (Scheme 133).[157] Chloroglyoxime **303** and an excess of thionyl chloride were refluxed together in ether. Distillation at water aspirator pressure (b.p. 48-50°C @ 15 mmHg) followed by precipitation of cyanoformhydroximoyl chloride from the distillate by the addition of hexane, yielded the target compound in 31% yield.



303 **304**

Scheme 133: Reagents: (i) $SOCl_2$, ether

Carbon-13 NMR spectroscopy identified the two carbon atoms in the structure (Table 12).

Table 12: The ^{13}C NMR spectroscopic data of 304

$\delta_{C(ppm)}$	
C(Cl)=N	111.1
C≡N	115.2

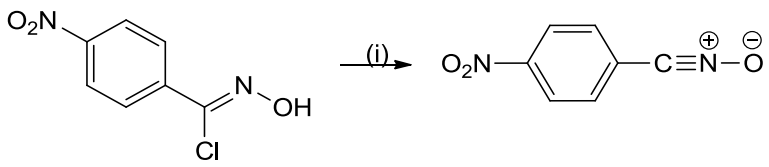
The IR spectrum of **304** also supports the structure. A strong broad signal at 3234 cm^{-1} was assigned to the –OH stretch. Characteristic nitrile and imine stretches were observed at 2243 and 1624 cm^{-1} respectively. The ESI^+ mass spectrum in negative ion mode confirmed the molecular mass of the compound (M^-, 103, 100%).

1.2 Generation of nitrile oxides

Nitrile oxides are liberated from their hydroximoyl halide precursor by the addition of a base. The IR spectra of a number of nitrile oxides were reported by Wakefield *et al*, who identified absorption bands at 2295 cm^{-1} and 1370 cm^{-1} as '*characteristic of the triple bond and the N-oxide linkages of the nitrile oxide group*'.[165] Wakefield *et al.* chose aqueous sodium carbonate as the base for dehydrohalogenation of the hydroximoyl chloride precursor to liberate 3,5-dichlorobenzonitrile-*N*-oxide. The nitrile oxide was reacted immediately with a dipolarophile, therefore it was not isolated or characterised (other than to note that the IR spectrum did not have a typical for CNO absorption).

1.2.1 *p*-Nitrobenzonitrile-*N*-oxide

The first method that we employed to generate a nitrile oxide in solution utilised NMR spectroscopy as the analytical method. Combining a solution of the hydroximoyl chloride **275** in chloroform-*d* with a solution of triethylamine in the same solvent allowed for quick transferral of the solution into an NMR spectroscopy tube. The triethylammonium hydrochloride produced in the reaction is soluble in chloroform-*d*, therefore facilitating efficient analysis.



275 **265**

Scheme 134: Reagents: (i) NEt_3, ethanol, < 0 °C

Evidence for the nitrile oxide **265** was observed in the proton and carbon-13 NMR spectra of the solution - characteristic signals are shown in Table 13. The signals for *o*–Ar-C and *m*-Ar-C shifted from 8.05 and 8.31 ppm in the hydroximoyl chloride to 7.73 and 8.31 ppm in the nitrile oxide. The absence of the broad singlet in the proton NMR spectrum of the nitrile oxide at 13.01 ppm (-OH of hydroximoyl chloride) confirms that the hydroximoyl chloride was consumed.

Table 13: The ^{1}H and ^{13}C NMR spectroscopic data of 265

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
ArH	7.73	**C≡N**	119.6
ArH	8.31	**ArCH**	123.4 and 132.1

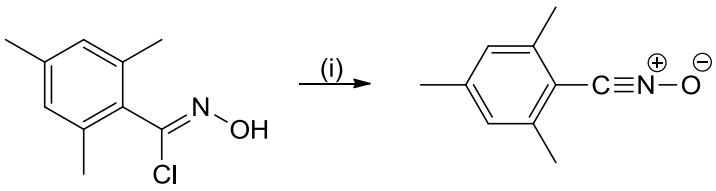
For a preparatory scale preparation of *p*-nitrobenzonitrile oxide **265**, ethanol was used in place of chloroform as per the procedure outlined by Eloy *et al.* (Scheme 134*)*. The nitrile oxide was generated as an isolable, relatively stable solid and was isolated in 91% yield as a pale yellow solid.[145l] Its melting point (92-93 ^{o}C) compares well with the literature value. The spectra of the crystalline nitrile oxide followed those observed for the compound in solution.

Balsamini *et al.* note that the half-life of *p*-nitrobenzonitrile oxide is one month at room temperature in ether.[54] According to our experience, the lifetime of the compound is *ca.* 15 h

in chloroform-*d* at room temperature. It is considerably more stable when stored as a solid in a freezer (up to 303 days).

1.2.2 Mesitonitrile-*N*-oxide

Mesitonitrile-*N*-oxide **7** was produced by adding a solution of the hydroximoyl precursor **281** to a stirring solution of triethylamine in ether (Scheme 135). The use of ether as the solvent facilitates the ease of removing the triethylamine hydrochloride precipitate that forms during dehydrohalogenation of the hydroximoyl chloride. Stirring the solution at room temperature for 2 h gave the nitrile oxide **7** in excellent yield following isolation of the triethylammonium chloride precipitate by filtration. While the melting point of crude **281** was ten degrees lower than the literature melting point, the solid did melt over a narrow range which is indicative of a relatively pure compound.[14d] The spectroscopic properties obtained correlate well with the literature, with the δ_C of the nitrile carbon observed at 141.7 ppm.[14i] The stability of this nitrile oxide in deuterated chloroform is 15 days.

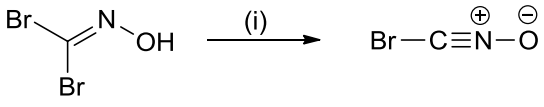


281 **7**

Scheme 135: Reagents: (i) NEt_3, ether

1.2.3 Bromoformonitrile-*N*-oxide

Bromoformonitrile-*N*-oxide **13** was initially generated by the addition of the hydroximoyl bromide **41** to a stirring solution of triethylamine in ether (Scheme 136). The nitrile oxide **13** was isolated as a white solid in 51% yield following evaporation of the filtrate. A shift of δ_C from 99.2 ppm in the bromooxime to 97.6 ppm in the nitrile oxide supports the formation of **13**.



41 **13**

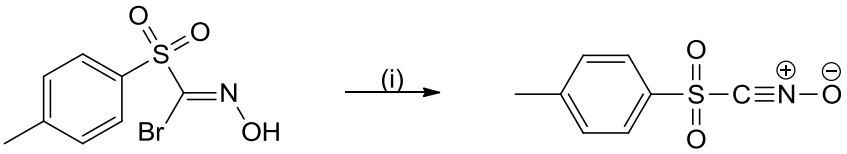
Scheme 136: Reagents: (i) NEt_3, ether

The reaction solvent can also play a part in the dehydrohalogenation of **41**. Herdewijn *et al.* found difficulty in generating the nitrile oxide of dibromoformaldoxime **41** when the reaction was carried out in THF.[145f] They used wet ethyl acetate and sodium bicarbonate to generate the nitrile oxide, as did Sala *et al.*.[166] Other than characterisation of the cycloaddition products, no other evidence for the generation of the bromonitrile oxide is provided by these researchers.

1.2.4 *p*-Toluenesulfonylformonitrile-*N*-oxide

The benefit of generating a benzenesulfonyl substituent on the heterocycle cycloadduct, is that it was '*easily substituted by a variety of nucleophiles*'.[167] Wade *et al.* explored this benefit by using benzenesulfonylnitrile oxide to generate the benzenesulfonyl substituent on the heterocycle. They attributed the high reactivity of benzenesulfonylnitrile oxide to synergistic electronic and steric factors: electron attracting substituents are known to increase the reactivity of other 1,3 dipoles toward alkenes and presumably this is one function of the benzenesulfonyl substituent. Also, its bulk is expected to retard the nitrile oxide dimerization.[51b]

Successful dehydrobromination of 1-*p*-toluenesulfonyl-1-bromoformaldoxime **299** proved to be more challenging than originally anticipated (Scheme 137).

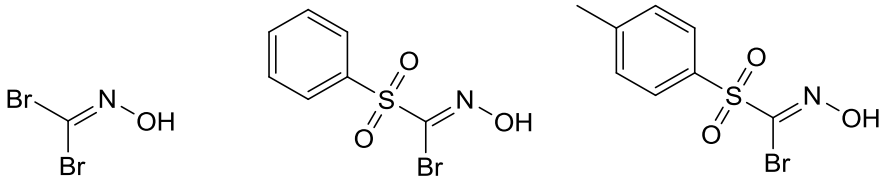


299 **307**

Scheme 137: Reagents: (i) Base, ether

The literature discusses the dehydrohalogenation challenge in relation to dibromoformaldoxime **41** and benzenesulfonyl-1-bromoformaldoxime **308**.[51b,145e,f] Wade *et al.* used potassium carbonate and sodium carbonate to release the nitrile oxide from dibromoformaldoxime **41** and benzenesulfonyl-1-bromoformaldoxime **308** (Figure 51). Wigerinck *et al.* used sodium bicarbonate to produce bromonitrile oxide from **41**. Extrapolating from this, we used a range of bases in the attempt at forming the nitrile oxide **307**: potassium hydrogen carbonate, potassium carbonate, DBU, triethylamine and potassium *t*-butoxide. The bases were screened using the same procedure on a 1 mmol scale: the base

was added to 1-*p*-toluenesulfonyl-1-bromoformaldoxime **299** in chloroform at room temperature.

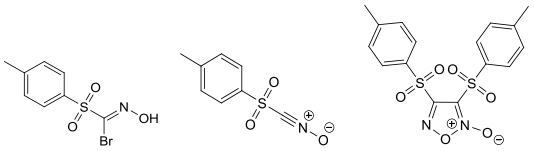


41 **308** **299**

Figure 51: Hydroximoyl halides that proved difficult to dehydrohalogenate

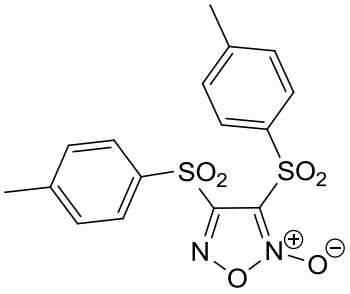
Chloroform was chosen as the NMR spectroscopic analysis was carried out in $CDCl_3$ and this avoided masking of NMR signals in the NMR spectrum. The resulting solution was stirred for five minutes and the putative nitrile oxide was isolated following an aqueous wash. The results of the screening process are summarised in Table 14.

Table 14: The results of the base screening process

Method[1]	**Base**	**Product(s)**  **299** **307** **309**
3	$KHCO_3$	Predominantly **299** with a trace of **307** and **309** evident
4	K_2CO_3	**299** 0% : **307** 54% : **309** 46%
5	DBU	Mixture of unidentifiable compounds
6	NEt_3	Mostly **309**
7	KO^tBu	Mostly **299** with a trace of **309**

Potassium carbonate and triethylamine were selected as the best bases to use for the dehydrohalogenation of the bromooxime **299**. We did note, however, that in any intended future cycloaddition reactions that the dipolarophile would have to be present in the reaction mixture prior to the addition of base to ensure that the nitrile oxide could be efficiently trapped to give an optimum yield and minimise the formation of the furoxan **309** (Figure 52).

[1] For methods 1-7, please see section 5.1.4 in Chapter 3.



309

Figure 52: Structure of 3,4-*bis*-(*p*-toluenesulphonyl)-furoxan 309

Figure 53 shows the proton NMR spectra correlating to these screening reactions:

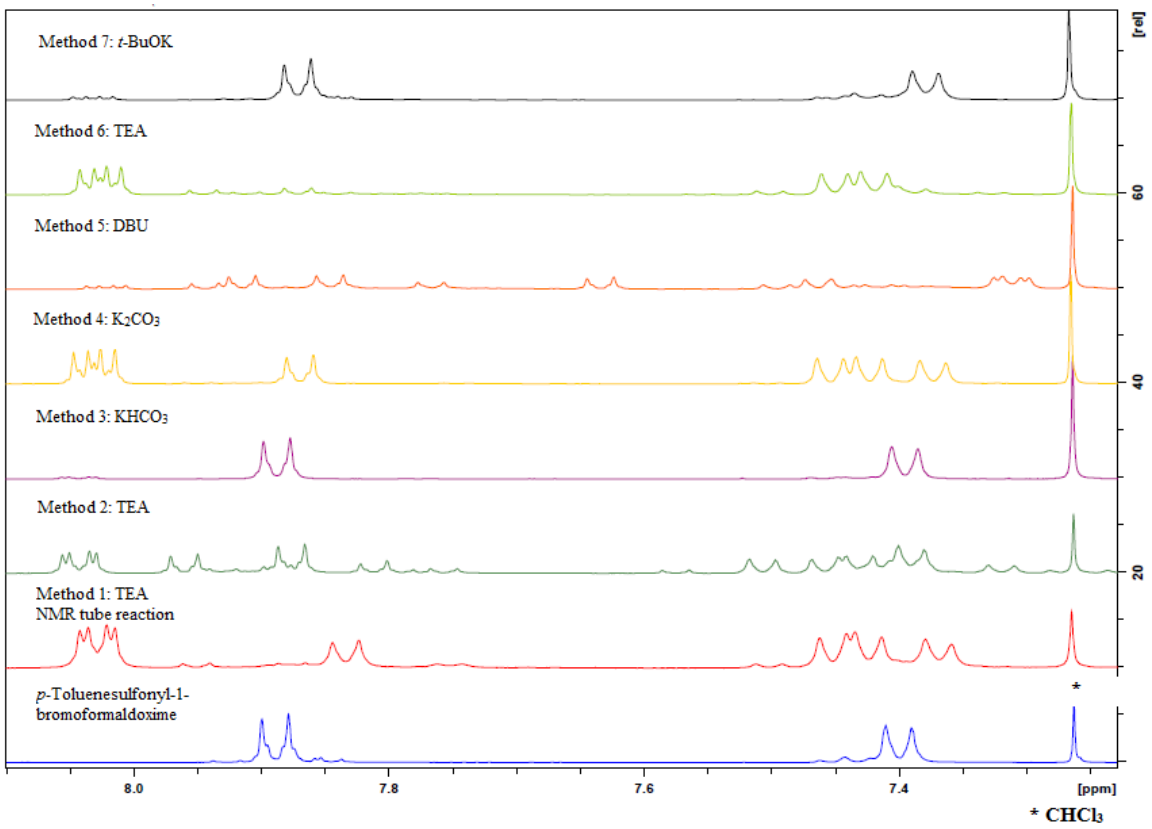
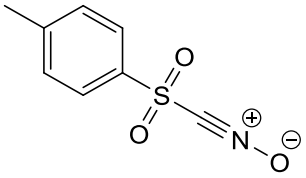


Figure 53: The ^{1}H NMR spectroscopic analysis using different bases to generate nitrile oxide 307

The scale of the reaction was increased to 3.0 mmol and triethylamine was used as the base (Method 2). Ether was the solvent used as the triethylamine hydrobromide precipitate was easily removed by filtration. Following ten minutes stirring at room temperature, ^{1}H NMR spectroscopic analysis showed that not all of the hydroximoyl bromide **299** was fully dehydrohalogenated, but **299**, the nitrile oxide **307** and furoxan **309** were evident in a ratio of 49 : 21 : 30.



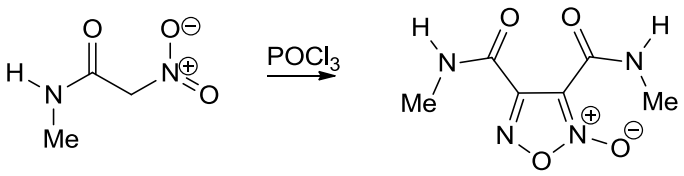
307

Figure 54: The nitrile oxide 307

Dipole generation was followed by NMR spectroscopy in chloroform-*d* on a 0.07 mmol scale (Method 1). Triethylamine was selected as the base. ^{1}H NMR spectroscopic analysis showed that total dehydrohalogenation had taken place, under these conditions, within ten minutes of adding the base to the halide in the NMR spectroscopy tube. In addition to triethylamine hydrobromide, formation of the nitrile oxide **307** and the furoxan **309** was evident from the spectra.

1.3 Preparation of furoxans

To definitively assign the peaks in the ^{1}H NMR spectra of the nitrile oxides prepared, reference samples of their dimers (furoxans) were prepared. The preparation of 3,4-disubstituted 1,2,5-oxadiazole-2-oxides (furoxans) is typically achieved *via* dimerisation of nitrile oxides.[12h,12k,l,12n,12p,165] Harris *et al.* discussed an alternative from nitroacetamides.[41] During an attempt to convert *N*-methyl nitroacetamide **310** into its iminochloride, it was treated at room temperature with phosphorous oxychloride. The furoxan **311** was isolated as the only reaction product (Scheme 138).

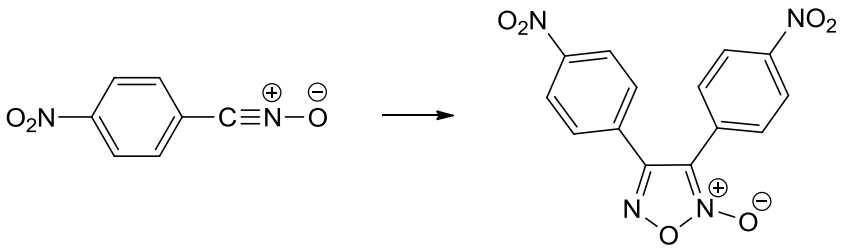


310 **311**

Scheme 138: Conversion of *N*-methyl nitroacetamide 310 into its iminochloride

As outlined above, the first method of preparing *p*-nitrobenzonitrile-*N*-oxide **265** involved its generation from *p*-nitrobenzohydroximoyl chloride **275** in $CDCl_3$ in an NMR spectroscopy tube. This solution was monitored over time to view the formation of the furoxan **312** (Scheme 139). Dimerisation of the nitrile oxide in solution was complete in $CDCl_3$ within 15 h at room temperature and its ^{1}H NMR spectroscopic analysis was in agreement with that

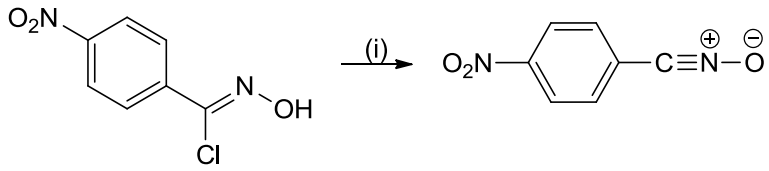
reported by Krishnamurthy *et al.*.[12l] Ben Hadda *et al.* have determined the single crystal X-ray structure of the furoxan **312**.[12m]



265 **312**

Scheme 139: Dimerisation of nitrile oxide 265 to the corresponding furoxan 312

A synthetic scale reaction was the second method employed in generating the nitrile oxide **265**. The dehydrohalogenation of the hydroximoyl chloride **275** precursor was carried out in ether with triethylamine as the base (Scheme 140). A sample of *p*-nitrobenzonitrile-*N*-oxide **265** was dissolved in $CDCl_3$ and monitored by ^1H NMR spectroscopy. Within 1.25 h in solution, dimerization to the furoxan began to take place. This experiment confirmed that within 17.75 h, the nitrile oxide component of the NMR spectroscopy sample had completely dimerised. The spectra showed a complete absence of the δ_H signals at 7.73 and 8.31 ppm for nitrile oxide **265**.



275 **265**

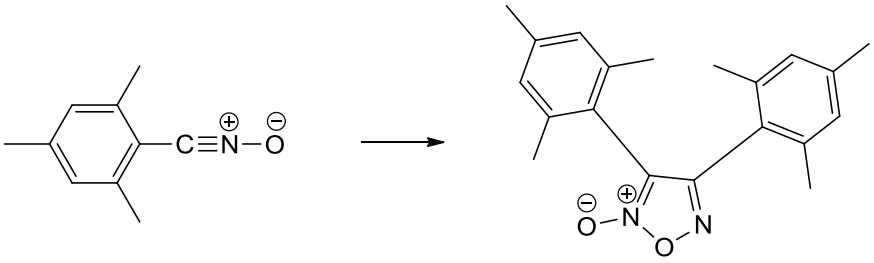
Scheme 140: The conversion of 275 to 265

The nitrile oxide sample, a pale yellow solid, was stored in a freezer over time and was analysed periodically (refer to previous section *p*-nitrobenzonitrile-*N*-oxide). A fresh sample was analysed in each case, in a chloroform-*d* solution, and it was found that the nitrile oxide could be stored without any decomposition at -23 ^oC for 303 days (analysis was stopped at this point, so technically it may be stored for longer than this time!).

1.3.1 Dimesitylfuroxan

Evidence for the furoxan **313** of mesitonitrile-*N*-oxide **7** was collected during an experiment using NMR spectroscopy (Scheme 141). The solution of mesitonitrile-*N*-oxide **7** in

chloroform-*d* at r.t. was monitored over time for dimerization and dimerisation was complete within 15 days. Mesitonitrile-*N*-oxide **7** is regarded as a kinetically stable nitrile oxide[12a,15] and proved to be more stable than all other nitrile oxides encountered during the course of this research.



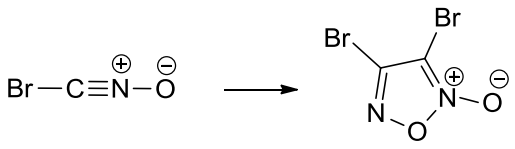
7 **313**

Scheme 141: Dimerisation of nitrile oxide 7 to the corresponding furoxan 313

Dimesitylfuroxan-*N*-oxide was not observed by Grundmann *et al.*.[12d] Their '*attempts to force the dimerization to furoxans by heating the nitrile oxides above their melting point or by refluxing them in a high boiling solvent, such as xylene or decalin, have resulted in a clean rearrangement to the corresponding isocyanates with no furoxan formation*'. The spectroscopic data for dimesitylfuroxan-*N*-oxide **313** has not appeared in the literature.

1.3.2 Dibromofuroxan

Spectroscopic signals of dibromofuroxan **15** were observed when a solution of **13** was allowed to stand in chloroform-*d* at r.t. for 7 days (Scheme 142). The initial ^{13}C NMR spectrum, shows the nitrile oxide peak at δ_C 99.1 ppm as a sharp singlet. In the next spectrum (t = 17.75 h), the original sharp singlet at 99.1 ppm appears to broaden. In subsequent spectra (t = 144 h), the peak at 99.1 ppm has completely disappeared and in its place are two single peaks at 97.9 and 98.0 ppm (Figure 55), therefore, indicating the change from nitrile oxide (having one single C signal) to the furoxan (having two C signals). The shift in ppm also indicates the change of environment of the C signals.



13 **15**

Scheme 142: Dimerisation of bromonitrile oxide 13 to dibromofuroxan 15

Hagedorn *et al.* reported the isolation of dibromofuroxan **15** by ether extraction.[17] As no solid precipitate was seen while the furoxan was in solution, chloroform could also be an example of a solvent in which the furoxan is soluble. Sennewald *et al.* reported the formation of the furoxan **15** but no physical or spectroscopic data was given.[168]

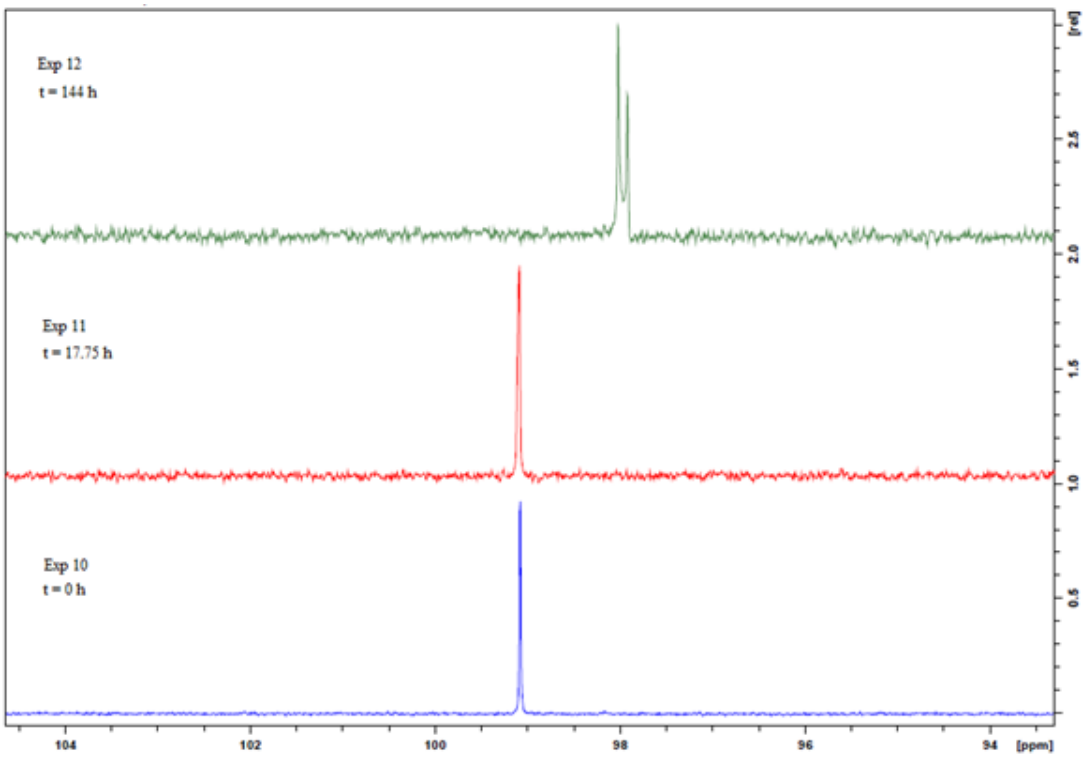
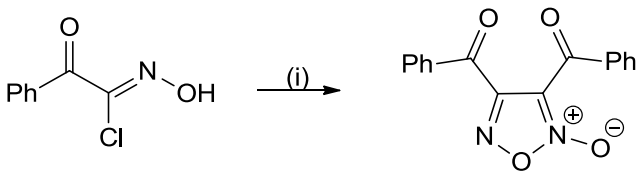


Figure 55: A time series of the ^{13}C NMR spectroscopic analysis ($CDCl_3$, 600MHz) illustrating the dimerisation of bromonitrile oxide 13 to dibromofuroxan 15

1.3.3 3,4-Dibenzoylfuroxan

Generation of the furoxan **314** was carried out by adding triethylamine to a stirring solution of **286** in ether at room temperature (Scheme 143). The solution was stirred overnight and the dimer **314** was isolated as a yellow crystalline solid in 78% yield.



286 **314**

Scheme 143: Reagents: (i) NEt_3, ether

Its melting point (77.5-80.5 ^{o}C) correlated with the literature value.[12f] Boyer *et al.* reported the infrared '*vibrations*' at 1620, 1475, 1330, 1188, 1030, 930 and 850 cm $^{-1}$ in 1955, which

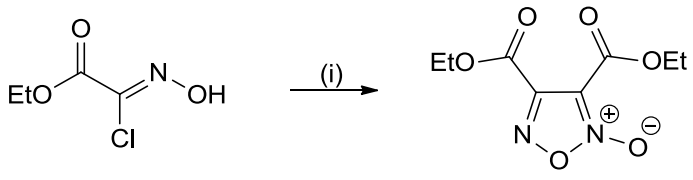
parallels the research by Engberts *et al.* and correlates with the experimental data we obtained for **314**. [12v,12x] The molecular ion species was observed at m/z = 295 under ESI^+ conditions and its spectroscopic data is outlined in Table 15, which is in agreement with the literature.[169]

Table 15: The ^1H and ^{13}C NMR spectroscopic data of 314

$\delta_{H(ppm)}$			$\delta_{C(ppm)}$	
ArH	4H, m	7.55	**4 x ArCH**	129.1, 129.2, 129.7 and 130.6
ArH	2H, m	7.70	**2 x *p*-ArCH**	128.5 and 130.2
ArH	2H, m	7.86	**2 x *i*-ArCH**	135.2 and 135.5
ArH	2H, m	8.20	**2 x C=N**	154.3 and 170.7
-			**2 x C=O**	180.4 and 181.8

1.3.4 3,4-Diethoxycarbonylfuroxan

The furoxan **315** was produced by reacting its hydroximoyl halide precursor **295** with triethylamine as the base (Scheme 144). The reaction mixture was stirred at room temperature for 1 h and the solution was filtered to remove the triethylammoniun chloride precipitate. On evaporation of the solvent, no product was isolated, indicating that the furoxan **315** had in fact precipitated from the ether with the amine hydrochloride. Dissolving the solid in dichloromethane and washing the resulting solution with water served to separate the triethylammonium chloride from the furoxan **315**. The latter was isolated as a yellow oil in 90% yield, which is consistent with the description by Kornblum *et al.*.[12n]



295 **315**

Scheme 144: Reagents: (i) NEt_3, ether

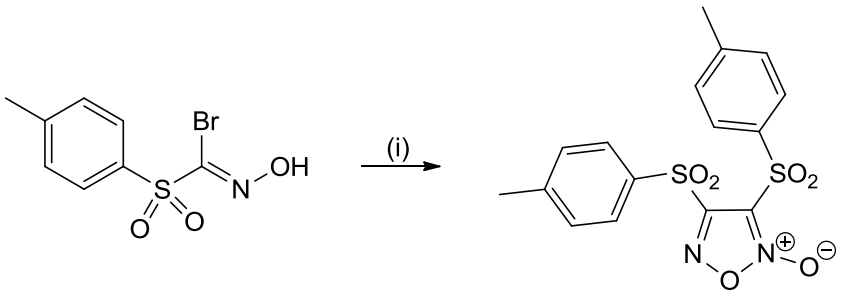
The spectroscopic properties of the compound we isolated correlate well with the structure (Table 16) and those outlined in the literature.[12n,12v,170] While Trogu *et al.* recorded two signals in the region of 13.5 ppm in the carbon-13 NMR spectroscopy, we observed these signals at 8.6 and 13.9 ppm. Its molecular ion was observed at 231.0621 [$(M+H)^+$] under ESI^+ conditions.

Table 16: The ^{1}H and ^{13}C NMR spectroscopic data of 315

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
2 x C$\underline{H}_3$	1.42	**2 x $\underline{C}H_3$**	8.6 and 13.9
2 x C$\underline{H}_2$	4.48	**2 x $\underline{C}H_2$**	43.8 and 63.6
-		**2 x $\underline{C}$=N**	106.7 and 148.4
-		**2 x $\underline{C}$=O**	155.1 and 156.7

1.3.5 3,4-*bis*-(*p*-Toluenesulfonyl)-furoxan

The furoxan **309** was generated by reacting its hydroximoyl halide precursor **299** with triethylamine as the base (Scheme 145).



299 **309**

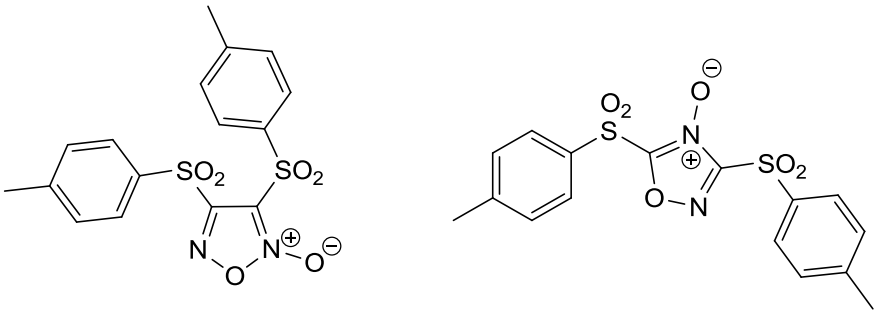
Scheme 145: Reagents: (i) Triethylamine, ether

The resulting solution was stirred overnight at room temperature and following filtration, the furoxan **309** was isolated in 29% yield as an orange solid. Its melting point (155-158 ^{o}C) did not correlate well with the literature data for the product (181-183 °C), however the infrared spectra showed '*typical furoxan absorptions*' at 1619, 1492 and 1449 cm^{-1}.[12g,12w,x] The proton NMR spectroscopic data for the furoxan **309** sample is consistent with its molecular structure (Table 17).

Table 17: The ^{1}H and ^{13}C NMR spectroscopic data of 309

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
2 x ArC$\underline{H}_3$	2.49	**3 x ArC$\underline{C}H_3$**	21.4, 21.5 and 22.0
Ar$\underline{H}$	7.42	**8 x Ar$\underline{C}$H**	126.0, 126.5, 129.1, 129.3, 129.7, 130.3 and 130.5
Ar$\underline{H}$	7.80	**$\underline{C}$=N**	147.5
Ar$\underline{H}$	7.96	-	
Ar$\underline{H}$	8.04	-	

Subsequent carbon-13 spectroscopic analysis, which was collected two years after initial NMR spectroscopy analysis, suggests that the product was a mixture of **309** and the asymmetric 1,2,4-oxadiazole-4-oxide **316** (Figure 56).



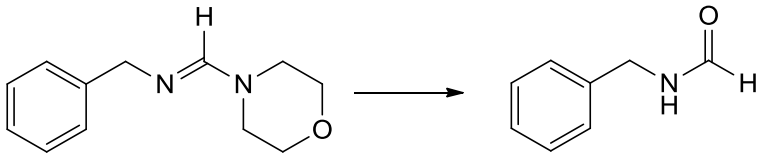
309 **316**

Figure 56: Symmetric furoxan 309 and asymmetric 1,2,4-oxadiazole-4-oxide 316

2 Reference compounds

2.1.1 *N*-Benzylformamide

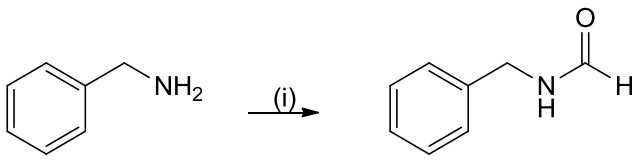
N´-Benzylformimidoylmorpholine **318** was degrading during the cycloaddition reaction and was believed to be forming *N*-benzylformamide **319** (Scheme 146).



318 **319**

Scheme 146: Degradation of 318 to 319

For the purpose of comparison, amide **319** was prepared by heating benzylamine to reflux in neat ethyl formate (Scheme 147). *N*-Benzylformamide **319** was isolated in 83% yield as a white solid following recrystallization from toluene. The melting point (63-65 ^{o}C) was in excellent correlation with the literature, as was the spectroscopic data. ^{1}H NMR spectroscopic evidence for both rotamers was observed with a ratio of minor:major (1:5).[171] Its molecular ion was observed at m/z = 136 $[M+H]^{+}$under ESI^{+} conditions.

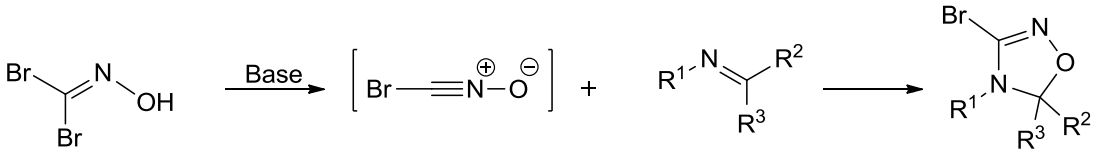


317 **319**

Scheme 147: Reagents: (i) Ethyl formate

2.2 Reference material for bromonitrile oxide cycloadditions

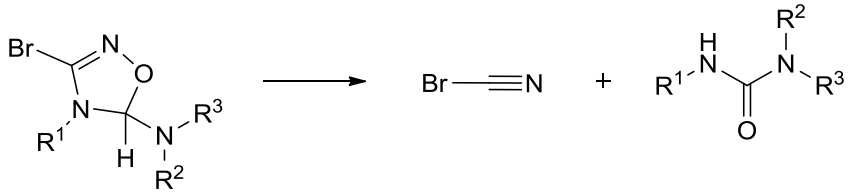
Scheme 148 illustrates the typical 1,3-dipolar cycloaddition reaction with dibromoformaldoxime **41** as the nitrile oxide precursor of **13**. This reaction was carried out with a number of dipolarophiles.



41 **13**

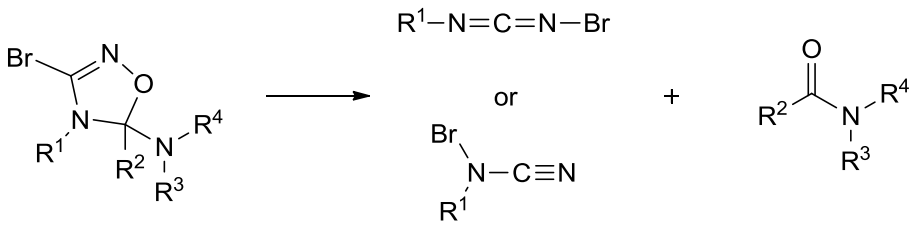
Scheme 148: 1,3-Dipolar cycloaddition reaction with dibromoformaldoxime 41 as the nitrile oxide precursor of 13 with a dipolarophile to form the Δ^2-1,2,4-oxadiazoline

Our initial work failed to isolate the Δ^2-1,2,4-oxadiazoline. Following previous studies by Hogan with related structures, the decomposition products were anticipated to be a nitrile and a urea (Scheme 149).[140]



Scheme 149: The expected decomposition products of a Δ^2-1,2,4-oxadiazoline

However, in the case of the bromonitrile oxide, our work established that this did not occur. Instead, an amide was isolated, leading to the belief that a different mechanistic pathway was operative (Scheme 150). A process proceeding through an imidoyl nitrene that would rearrange to a carbodi-imide was envisaged.

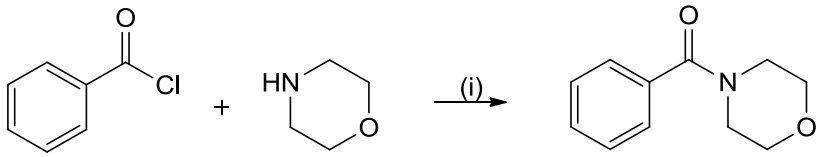


Scheme 150: The putative mechanistic pathway for the 3-bromo-Δ^2-1,2,4-oxadiazoline

In view of the plan to conduct cycloadditions of **13** with various amidines, we prepared several *N*-benzoyl amides as reference compounds.

2.2.1 *N*-Benzoylmorpholine

The amide **322** was synthesised by addition of an ethereal solution of morpholine **321** to benzoyl chloride **320** (also in ether) in the presence of triethylamine (Scheme 151). *N*-Benzoylmorpholine **322** was isolated as a white crystalline solid in 42% yield following dilution in hexane. Its melting point (67-69 ^{o}C) was a few degress lower than that observed in the literature but was still within an acceptable range.[172]



320 **321** **322**

Scheme 151: Reagents: (i) NEt_3, ether

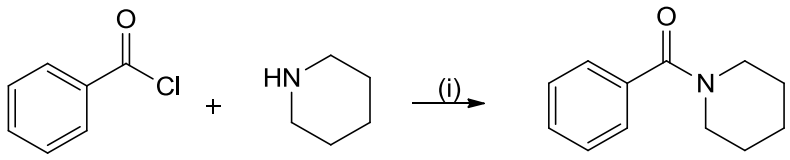
The infrared spectrum was in excellent accord with that reported by Ohshima *et al.*, as is the NMR spectroscopic data (Table 18). One discrepancy between the carbon-13 data we obtained and those reported by Ohshima *et al.*, was the clear signal we observed at δ_C 42.5 ppm for the carbons attached to the nitrogen of the morpholine group. There was not any mention of this signal in Ohshima's report. We observed the molecular ion at m/z = 192 $[M+H]^+$ under ESI^+ conditions.

Table 18: The ^{1}H and ^{13}C NMR spectroscopic data of 322

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
$N(CH_2)_4O$	3.60	**$N(\underline{C}H_2)_2$**	42.5
Ar<u>H</u>	7.41	**$O(CH_2)_2$**	66.9
-		***m*-Ar<u>C</u>H**	127.1
-		***o*-Ar<u>C</u>H**	128.6
-		***p*-Ar<u>C</u>H**	129.9
-		***ipso* <u>C</u> of Ar**	135.3
-		**<u>C</u>=O**	170.5

2.2.2 *N*-Benzoylpiperidine

The amide **324** was prepared by the reaction of benzoyl chloride **320** with piperidine **323** in the presence of triethylamine (Scheme 152). Ether was the reaction solvent. *N*-Benzoylpiperidine **324** was isolated in 79% yield as yellow oil.



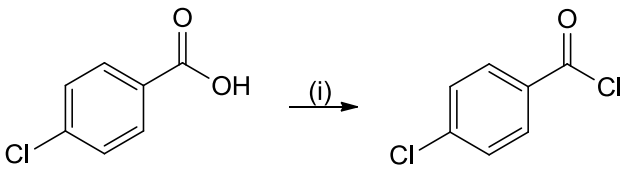
320 **323** **324**

Scheme 152: Reagents: (i) NEt_3, ether

The amide has been reported in the literature as a white solid, melting at 47-48 ^{o}C.[172] The infrared spectra supports the structure and is in agreement with that reported by Ohshima *et al.*.[172] The spectroscopic data was also in good agreement with the literature, except for the carbon spectra of the piperidine ring in particular. Hirsch *et al.* described the observed signals as 45.8 (α- to N), 26.1 (β- to N), 24.5 (γ- to N).[173] On the other hand, Ohshima *et al.* chronicled the piperidine ring as being represented by four signals: 48.66, 42.97, 26.08 and 24.58 ppm. The carbon spectra of the amide we synthesised showed five signals for the piperidine ring-one for each carbon 48.8, 43.1, 26.6, 25.6 and 24.6 ppm.

2.2.3 *N*-(*p*-Chlorobenzoyl) morpholine

The amide **327** was prepared from *p*-chlorobenzoic acid **325** in two steps *via* the acid chloride **326** which was available by reaction of the acid with thionyl chloride in dichloromethane (Scheme 153).

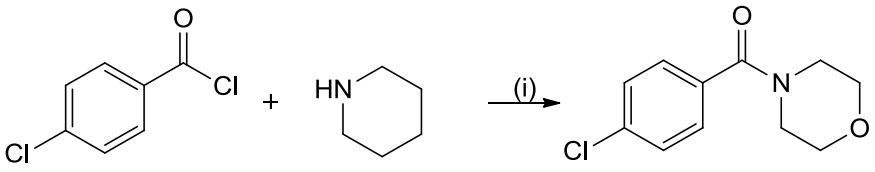


325 **326**

Scheme 153: Reagents: (i) Thionyl chloride, dichloromethane

Conversion to the pale yellow acid chloride **326** was confirmed by the loss of the IR absorption at 1677 $cm^{-1}$and the observation of the acid chloride peak at 1776 cm^{-1}. The compound was used directly in the next step without further purification.

The amide **327** was generated by the combination of the acid chloride **326** with morpholine in the presence of triethylamine, in ether (Scheme 154). *N*-(*p*-Chlorobenzoyl) morpholine **327** was isolated as a white solid in 77% yield (over two steps).



326 **321** **327**

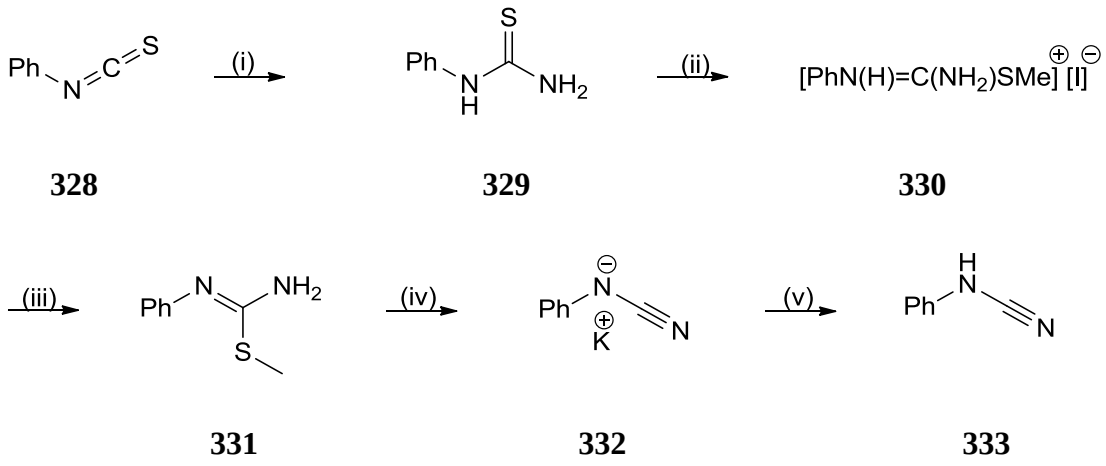
Scheme 154: Reagents: (i) NEt_3, ether

Its melting point (73-74 ^oC) was within the range of that reported in the literature.[174] The proton and carbon spectroscopic data was in good agreement with that reported by Shen *et al.* and the molecular ion was observed at m/z = 226 [M+H, $^{35}Cl]^+$ under ESI^+ conditions.

2.2.4 Phenylcyanamide

The products from certain cycloaddition reactions did not follow the nitrile-urea route, but instead produced an amide plus another material. A sharp peak observed at ~2220 cm^{-1} in the IR spectra suggested a cumulene (N=C=N) or nitrile type structure. We synthesised phenylcyanamide from potassium phenylcyanamide in an effort to ascertain if it could be the other reaction product.

Thioureas may be prepared by the Meckler synthesis, which is based on the condensation of amine hydrogen halides with potassium thiocyanate (Scheme 155).[175] This route is useful in the synthesis of primary thioureas and symmetrical *N*,*N*´-disubstituted thioureas.



Scheme 155: (i) Ammonia, dichloromethane; (ii) Iodomethane, acetone; (iii) Ammonia, IPA; (iv) potassium hydroxide, DIW, IPA; (v) 2 M HCl

Initially, *α*-phenylisothiourea **329** was synthesised using the method of Batey *et al.*.[176] This was achieved by adding phenylisothiocyanate to a stirring solution of ammonia in dichloromethane. An aqueous work-up followed with the phenylisothiourea being extracted into dichloromethane. Recrystallisation from dichloromethane-hexane afforded *α*-phenylisothiourea **329** in 63% yield and its m.p. (154-155 ^{o}C) was in excellent correlation with the literature.[177]

Methyl-*N*-phenylcarbamidothioate hydroiodide **330** was then generated following Cohen's procedure by adding iodomethane to a stirring solution of phenylisothiourea in acetone.[178] Washing the solid residue with ether afforded the product as a pale cream solid in 95% yield. Its m.p. (145-145.5 ^{o}C) indicated good purity and was in agreement with the literature m.p. (140 ^{o}C).[177] The methyl-*N*-phenylcarbamidothioate hydroiodide **330** was then reacted with ammonia and gave *N*-phenyl-*S*-methylisothiourea **331** in 82% yield. Its m.p. (63-65 ^{o}C) and spectroscopic data agreed with the literature (72 ^{o}C). Potassium phenylcyanamide **332** was generated from **331** by the procedure of Schultz *et al.*. This involved addition of potassium hydroxide to *N*-phenyl-*S*-methylisothiourea **331**. The resulting solution was heated at reflux and the product precipitated from solution as a white solid. Recrystallisation from acetone afforded the salt as a white solid in 42% yield. Its m.p. (328 ^{o}C, decomp.) is in good correlation with the literature (345 ^{o}C). Phenylcyanamide **333** was available[177] by neutralisation of **332** with 2 M HCl and isolated as a pale yellow oil in 96% yield. The IR spectrum with the characteristic peaks at 3100 cm^{-1} (-NH) and 2229 cm^{-1}(C≡N), reflects the literature data.

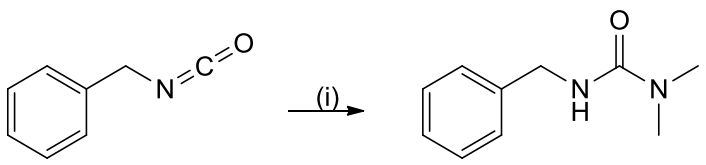
One of the reasons we believed phenylcyanamide **333** to be one of the potential conversion products was that the literature IR data of **333** showed an intense sharp peak observed at 2222 cm^{-1}.[177] The experimental data we report is in agreement with this literature data which was outlined by Schultz *et al.*. However, overlaying of the spectra of phenylcyanamide that we isolated with those of the spectra of the oxadiazoline reaction mixture showed that the peaks at ~2220 cm^{-1} did not quite correlate with each other.

2.3 Ureas

Early studies relating to the field of nitrile oxide-amidine cycloadditions did not permit isolation of Δ^2-1,2,4-oxadiazoline as the heterocycles involved were too unstable. Other studies by Hogan reported that the decomposition products were a nitrile and a urea.[140]As a number of Δ^2-1,2,4-oxadiazolines that were being prepared during our research work were novel compounds, the anticipated urea decomposition products were generated as a means to simplify interpretation of the NMR spectra by way of direct comparison.

2.3.1 1-Benzyl-3-(*N*,*N*-dimethyl)-urea

Benzylisocyanate **334** was added to a solution of *N*,*N*-dimethylamine in toluene at 70-80 ^oC to give the crude urea **335** as pale yellow oil (Scheme 156).



334 **335**

Scheme 156: Reagents: (i) *N*,*N*-Dimethylamine, toluene

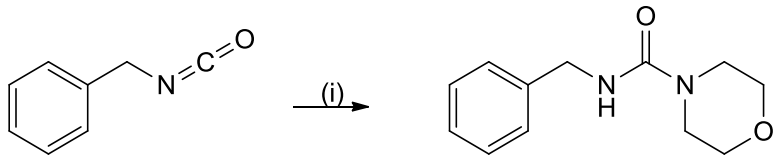
Recrystallisation of the latter from methanol gave 1-benzyl-3-(*N*,*N*-dimethyl)-urea **335** in 85% yield as a white solid. Its melting point (64-65 ^oC) was lower than that reported by Anastassiou *et al.*, but was still within range.[179] The NMR spectroscopic data is outlined in Table 19. The molecular ion was observed at m/z = 179 $[M+H]^+$under ESI^+ conditions.

Table 19: The ^{1}H and ^{13}C NMR spectroscopic data of 335

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
$N(C\underline{H}_3)_2$	2.92	**$N(\underline{C}H_3)_2$**	36.3
$PhC\underline{H}_2$	4.42	**$PhCH_2$**	45.1
N<u>H</u>	4.65	***p*-Ar<u>C</u>H**	127.3
Ar<u>H</u>	7.30	**2 x Ar<u>C</u>H**	127.8 and 128.6
-		***ipso* <u>C</u> of Ar**	139.7

2.3.2 *N´*-Benzylmorpholine-4-carboxamide

The urea **336** was prepared by the reaction of benzylisocyanate **334** with morpholine in toluene at 70-80 ^{o}C (Scheme 157).



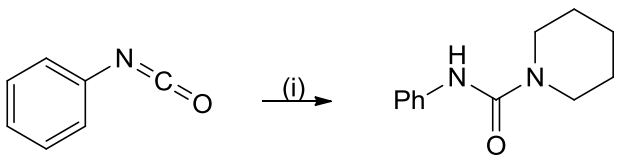
334 **336**

Scheme 157: Reagents: (i) Morpholine, toluene

N´-Benzylmorpholine-4-carboxamide **336** was isolated in 84% yield as a white crystalline solid. Its melting point (129-130 ^{o}C) was slightly higher than that reported in the literature, but the narrow range indicated reasonable purity.[180] The spectroscopic data is in good correlation with that of Peterson *et al.*.[181] The molecular ion was observed at m/z = 221 $[M+H])^{+}$ under ESI^{+} conditions.

2.3.3 *N*-Phenyl-1-piperidine carboxamide

The urea **337** was prepared by the addition of phenylisocyanate **338** to piperidine in toluene (Scheme 158).



338 **337**

Scheme 158: Reagents: (i) Piperidine, toluene

N-Phenyl-1-piperidine carboxamide **337** was isolated as a white solid in 90% yield. Its melting point (166-168 ^{o}C) is in excellent agreement with the literature, as is the spectroscopic data.[182] Its molecular ion was observed at m/z = 205 $[M+H]^+$ under ESI^+ conditions.

3 Preparation of dipolarophiles

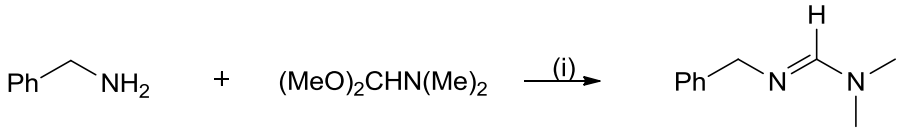
3.1 Formamidines

There are three sites in the amidine functional group to which substituents can be attached; the two nitrogen atoms and the amidine carbon atom.[68h] Substituents at both nitrogen atoms have considerable influence on the extent of conjugation. In general, the impact '*of a substituent at any site of the amidino group depends on substitution at the other two sites*'.

Choosing formamidines as the dipolarophile in the 1,3-dipolar cycloaddition with nitrile oxides to form Δ^2,1,2,4-oxadiazolines enabled exploration of subsitituents at the N4 and C5 position of the oxadiazoline. The formamidines selected during the course of this research investigated the effect on stability of the heterocycle when a phenyl, benzyl or *p*-chlorophenyl substituent was at the N4 position of the oxadiazoline. The formamdines targeted also gave an indication as to the effect on stability of the oxadiazoline when an *N*,*N*-dimethyl, morpholino or piperidino substituent is at the C5 position of the oxadiazoline.

3.1.1 *N*,*N*-Dimethyl-*N*´-benzylformamidine

N,*N*-Dimethyl-*N*´-benzylformamidine as a dipolarophile in a cycloaddition reaction would introduce a benzyl substituent at the N4 position of the resulting oxadiazoline and an *N*-alkyl substituent at the C5 position. *N*,*N*-Dimethylformamide dimethyl acetal **165** has already been used in the synthesis of amidines.[87a,183] *N*,*N*-Dimethyl-*N*´-benzylformamidine **339** was prepared by heating benzylamine with *N*,*N*-dimethylformamide dimethyl acetal **165** to reflux in methanol for 19 h (Scheme 159).



317 **165** **339**

Scheme 159: Reagents: (i) Methanol, reflux

The *amidine* **339** was isolated as a clear yellow oil following bulb to bulb distillation (b.p. 132-136 ^{o}C @ 15 mmHg) in 93% yield. Proton NMR spectroscopy exhibited the characteristic imine methine proton signal at 7.38ppm indicating that the formamidine had been produced. The spectroscopic data correlated excellently with the literature data (Figure 57).[184]

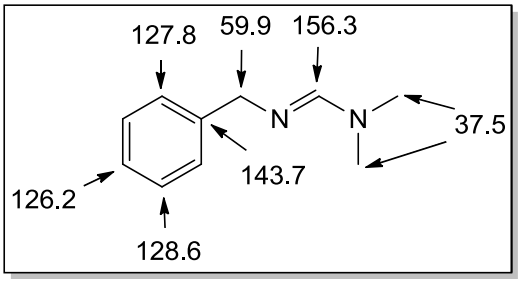
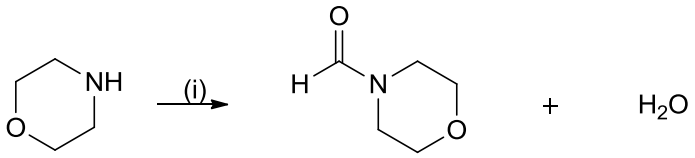


Figure 57: The ^{13}C NMR spectroscopic data of 339

3.1.2 *N´*-Benzylformimidoylmorpholine

N´-Benzylformimidoylmorpholine **318** as a dipolarophile in a cycloaddition reaction would introduce a benzyl substituent at the N4 position of the resulting oxadiazoline and a morpholine substituent at the C5 position. The synthesis of this formamidine is a two-step process: Firstly, *N*-formylmorpholine **340** is prepared and secondly, this formamide is coupled with benzylamine to yield *N´*-benzylformimidoylmorpholine **318**

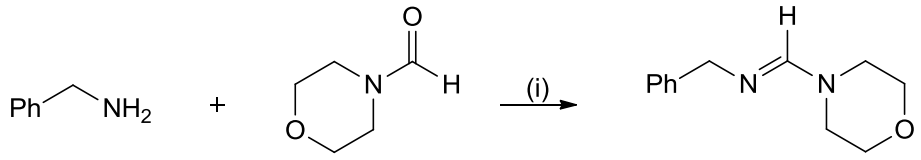
N-Formylmorpholine **340** was prepared by heating a solution of morpholine **321** with formic acid to reflux until all water (34.5 ml) was collected in a Dean-Stark trap (Scheme 160). The formamide **340** was purified by vacuum distillation (b.p. 112-114 ^{o}C @25 mmHg) and was isolated in 91% yield as a clear oil. ^{1}H NMR spectroscopic analysis of the product showed the formyl proton singlet at 8.06 ppm, which is consistent with literature values.[185]



321 **340**

Scheme 160: Reagents: (i) Formic acid, toluene

Preparation of *N´*-benzylformimidoylmorpholine **318** involved a Vilsmeier-type condensation of *N*-formylmorpholine **340** with benzylamine **317** in the presence of phosphorous oxychloride (Scheme 161)



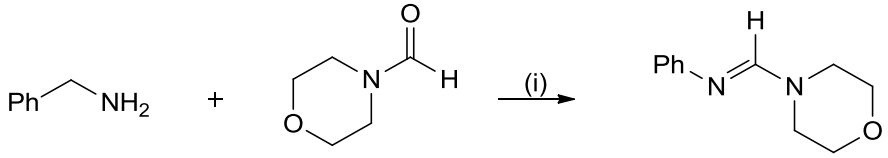
317 **340** **318**

Scheme 161: Reagents: (i) $POCl_3$, benzene.

The amidine **318** was isolated in 47% yield as a clear yellow oil following bulb-bulb distillation with a kugelröhr apparatus. The spectroscopic data of **318** correlates very well with the literature.[186]

3.1.3 *N*-Phenylformimidoylmorpholine

N-Phenylformimidoylmorpholine **341** was obtained following the addition of a solution of phosphorous oxychloride to a mixture of aniline and *N*-formylmorpholine **340** (Scheme 162).



317 **340** **341**

Scheme 162: Reagents: (i) Formic acid, toluene

The amidine **341** was isolated in 51% yield as a pale yellow crystalline solid following recrystallisation from ether : hexane. The amidine showed the same spectroscopic properties as those reported by previous researchers in the group with the imine singlet observed at δ_H 7.52 ppm.[140] Further spectroscopic techniques were used to examine this amidine. Sampling a solution of the amidine **341** in deuterated chloroform at 300K and at 323K yielded interesting results (Figure 58).

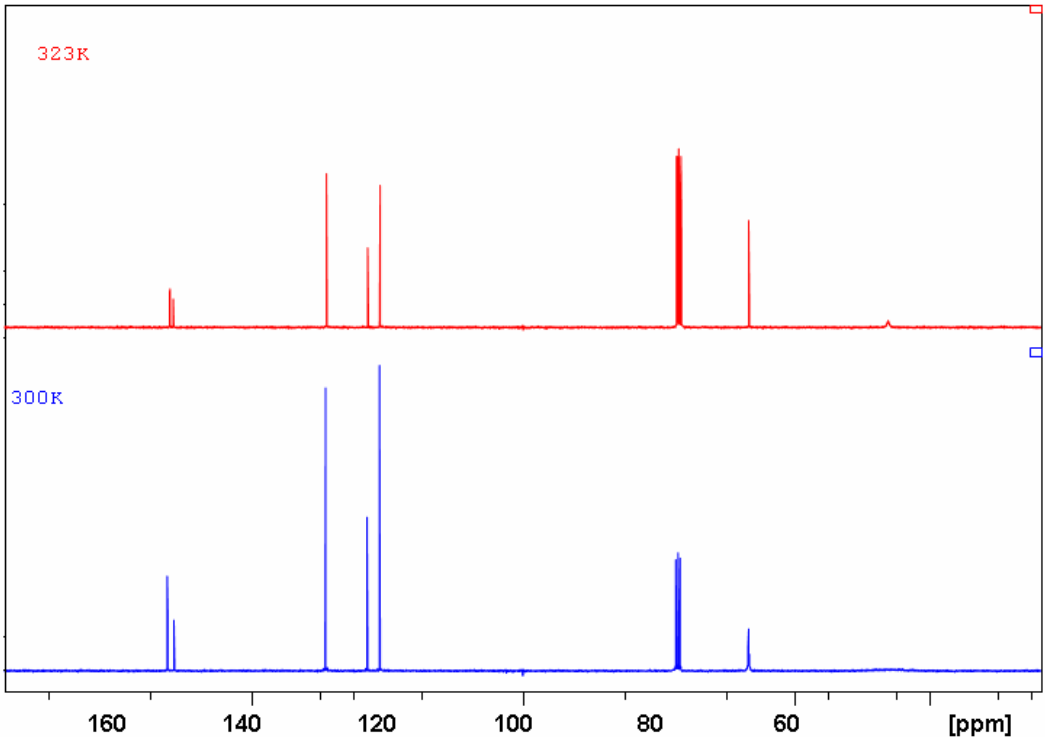
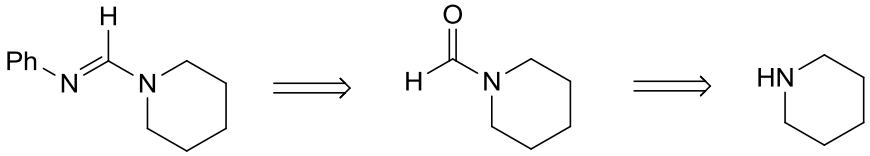


Figure 58: ^{13}C NMR spectroscopic data at two different temperatures of a solution of *N*-phenylformimidoylmorpholine 341 to illustrate the sharpening of the NCH_2 signal of the morpholine group at higher temperature

More typically, rotation around the single C-N bond is hindered by conjugation of the nitrogen lone pair of electrons with the carbonyl group.[184] Taking note of the signal for NCH_2, it appears as a broad singlet in the carbon spectra at 300K. However, increasing the temperature by 23 K shows a sharpening of the signal. At the higher temperature, rotation about the C-N bond is faster on the NMR spectroscopy time-scale and therefore, a sharpening of the signal occurs. The outcome suggests that 300K is the approximate coalescence temperature for the process.

3.1.4 *N*-Phenylformimidoylpiperidine

N-Phenylformimidoylpiperidine **343** was synthesised using a two-step approach. *N*-formylpiperidine **342** was firstly prepared and this was reacted with aniline to yield the amidine **343** (Figure 59).

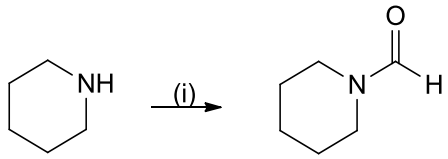


343 **342** **323**

Figure 59: Retrosynthetic analysis of amidine 343

3.1.4.1 *N*-Formylpiperidine

N-Formylpiperidine **342** was isolated in 70% yield following the reflux of a solution of formic acid with piperidine **323** in toluene (Scheme 163). The solution was refluxed until water that was collected had ceased.



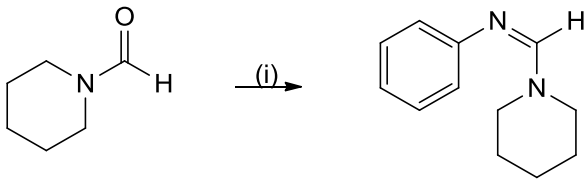
323 **342**

Scheme 163: Reagents: (i) Formic acid, toluene

The observed boiling point (74-99 ^{o}C @ 25 mmHg) was in accord with the literature.[187] The spectroscopic properties are in excellent correlation with the literature.[188] The formyl proton signal was observed at 8.00 ppm.

3.1.4.2 *N*-Phenylformimidoylpiperidine

The formamidine **343** was produced by combining *N*-formylpiperidine, phosphorous oxychloride and aniline in benzene and heating the resulting solution to reflux for 4 h (Scheme 164).



342 **343**

Scheme 164: Reagents: (i) Aniline, phosphorous oxychloride, benzene

N-Phenylformimidoylpiperidine **343** was isolated in 19% yield following recrystallization from chloroform:hexane as a pale yellow solid. The melting point (169-170.5 ^{o}C) differs with

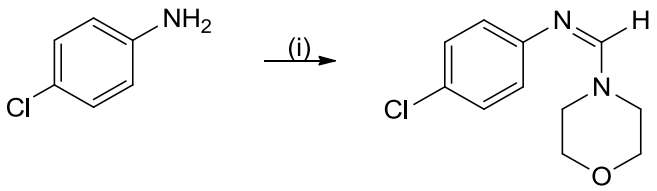
Seefelders who reported that **343** was isolated as an oil (b.p. 134-136 ^{o}C @ 0.5 mmHg)![189] The infrared spectrum was consistent with the molecular structure and its molecular ion $[M+H]^+$ was observed at m/z = 188 under ESI^+ conditions. NMR spectroscopic data is outlined in Table 20 and is in agreement with the structure of **343**.

Table 20: The ^{1}H and ^{13}C NMR spectroscopic data of 343

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
$(CH_2)_3$	1.69	**$N(CH_2)(CH_2)_3$**	23.2, 25.1 and 26.3
$N(CH_2)$	3.83	**$N(CH_2)$**	48.2
$N(CH_2)$	4.06	**$N(CH_2)$**	54.0
***p*-ArH**	7.17	***m*-ArCH**	119.7
***m*-ArH**	7.28	***p*-ArCH**	126.3
***o*-ArH**	7.70	***o*-ArCH**	129.5
N=CH	8.74	***i*-ArC**	137.3
-		**N=CH**	150.4

3.1.5 *N*-(*N´-p*-Chlorophenylformimidoyl)-morpholine

The formamidine **345** was prepared by heating a solution of *p*-chloroaniline **344**, morpholine and phosphorous oxychloride to reflux in benzene (Scheme 165).



344 **345**

Scheme 165: Reagents: (i) Morpholine, phosphorous oxychloride, benzene

N-(*N´-p*-Chlorophenylformimidoyl)-morpholine **345** was isolated in 63% yield as a grey crystalline solid following recrystallization from chloroform : hexane. It melted over a narrow range (66-67 ^{o}C) and its infrared spectra showed peaks that correlated to stretches in the molecule e.g. imine (C=N, 1632 cm^{-1}). Its molecular ion $[M+H]^+$ was observed at m/z = 225 under ESI^+ conditions. NMR spectroscopic data is outlined in Table 21.

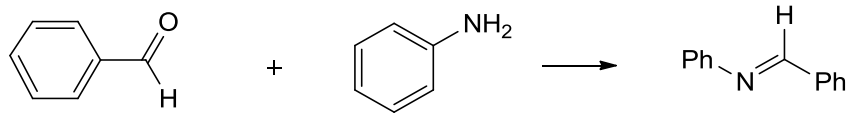
Table 21: The ^{1}H and ^{13}C NMR spectroscopic data of 345

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
N(CH$_2$)$_2$	3.52	**N(CH$_2$)$_2$**	45.8
O(CH$_2$)$_2$	3.74	**O(CH$_2$)$_2$**	66.7
***o*-ArH**	6.88	**2 x ArCH**	122.2 and 129.1
***m*-ArH**	7.21	***i*-ArC**	128.0
ArH	7.49	**ArC(Cl)**	150.1
-		**N=C**	152.3

3.2 Imines

3.2.1 *N*-Benzylideneaniline

Two methods were used to prepare *N*-benzylideneaniline **346** (Scheme 166). As this is a dehydration reaction involving an aldehyde and and amine, the water must be absorbed (method 1) or separated (method 2) from the reaction solution.



270 **172** **346**

Scheme 166: The preparation of *N*-benzylideneaniline 346

Benzaldehyde **270** and aniline **172** were used to make the imine with magnesium sulphate as the drying agent in the first method and a Dean-Stark apparatus was used to separate the water in the second method. Both methods gave the title compound in appreciable yield (89-99%), however the Dean-Stark apparatus gave the product in 99% yield. From a purity point of view, the melting point (49-50.5 ^{o}C) is in excellent correlation with the literature.[190] Spectroscopic data, both IR and proton NMR spectroscopic data correlate well with the literature. Details of the carbon-13 spectrum are given in Table 22:

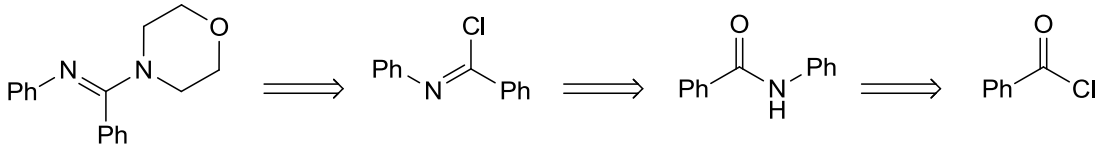
Table 22: The ^{13}C NMR spectroscopic data of 346

$\delta_{C(ppm)}$	
4 x ArCH	120.9, 128.8, 128.8 and 129.2
2 x *p*-ArCH	125.9 and 131.4
2 x *i*-ArCH	136.3 and 152.1
N=CH	160.4

3.3 Benzamidines

3.3.1 *N*-(*N*´-Phenylbenzimidoyl)-morpholine

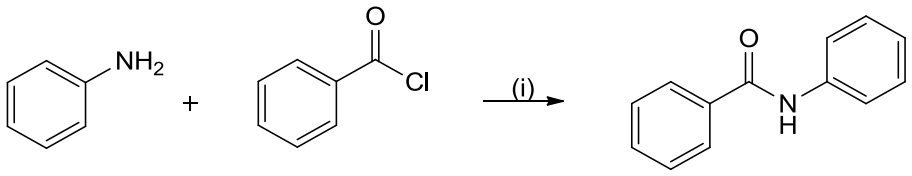
The synthesis of *N*-(*N*´-phenylbenzimidoyl)-morpholine **349** was a three-step process involving the preparation of *N*-benzoylaniline **347**, followed by its conversion to the corresponding imidoyl chloride, *N*-phenylbenzimidoyl chloride **348** (Figure 60). The crude imidoyl chloride **348** was subsequently combined with morpholine to yield the benzamidine *N*-(*N*´-phenylbenzimidoyl)-morpholine **349**.



349 **348** **347** **320**

Figure 60: Retrosynthetic analysis of benzamidine 349

N-Benzoylaniline **347** was prepared by stirring a mixture of benzoyl chloride **320** with aniline **172** and pyridine in THF overnight at room temperature (Scheme 167).

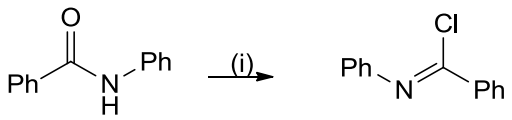


172 **320** **347**

Scheme 167: Reagents: (i) Pyridine, THF

The amide was isolated in 85% yield as a grey crystalline solid following recrystallization from ethanol. The melting point (166-168 ^{o}C) and spectroscopic properties of the compound agree with those reported in the literature.[191]

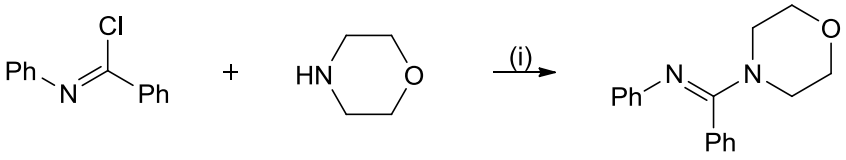
Heating *N*-benzoylaniline **347** with phosphorous pentachloride to reflux in toluene gave *N*-phenylbenzimidoyl chloride **348** which was used without further purification in the next step (Scheme 168).



347 **348**

Scheme 168: Reagents: (i) PCl_5, toluene

The freshly prepared imidoyl chloride **348** was combined with two equivalents of morpholine in ether and the resulting solution was stirred overnight at room temperature (Scheme 169).



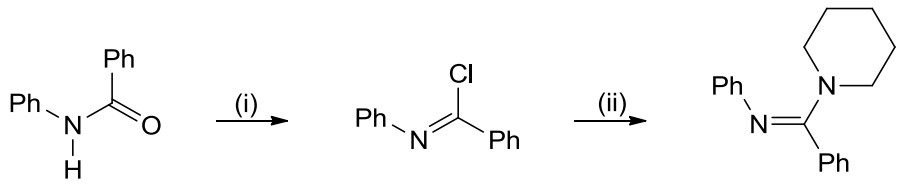
348 **321** **349**

Scheme 169: Reagents: (i) Ether

N-(*N´*-Phenylbenzimidoyl)-morpholine **349** was isolated in 53% yield (over two steps) as a pale orange crystalline solid following recrystallization from hexane. Its melting point (92-93 ^{o}C) is higher than that reported in the literature (88 ^{o}C), but as the solid melted over a relatively narrow range, we concluded that the amidine **349** had been isolated in a pure state.[192] The spectroscopic data correlates excellently with those reported in the literature and its molecular ion $[M+H]^+$ was observed at m/z = 267 under ESI^+ conditions.[193]

3.3.2 *N*-(*N´*-Phenylbenzimidoyl)-piperidine

N-(*N´*-Phenylbenzimidoyl)-piperidine **350** was prepared by combining piperidine with the crude imidoyl chloride **348** in ether and stirring the solution overnight (Scheme 170). *N*-Phenylbenzimidoyl chloride **348** could be prepared by heating *N*-benzoylaniline **347** with phosphorous pentachloride to reflux in toluene which was used without further purification in the next step. The amidine **350** was isolated in 57% yield (two steps) as yellow oil. Rappoport *et al.* isolated **350** as a colorless solid.[192]



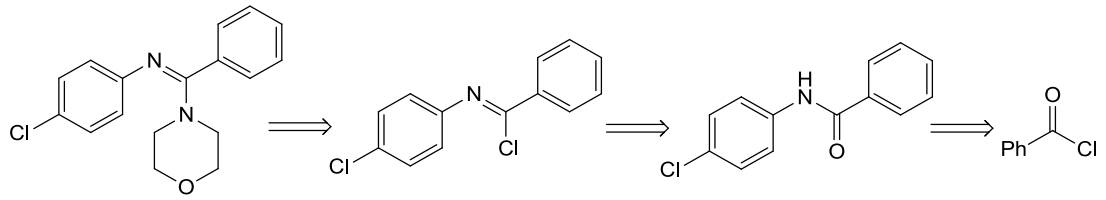
347 **348** **350**

Scheme 170: Reagents: (i) PCl_5, Toluene (ii) piperidine, ether

The spectroscopic data we obtained is in correlation with the literature, however, our spectra showed better resolution of the aromatic proton signals. The parent molecular ion $[M+H]^+$ was observed at m/z = 265.

3.3.3 *N*-(*p*-Chlorophenyl)-benzimidoyl morpholine

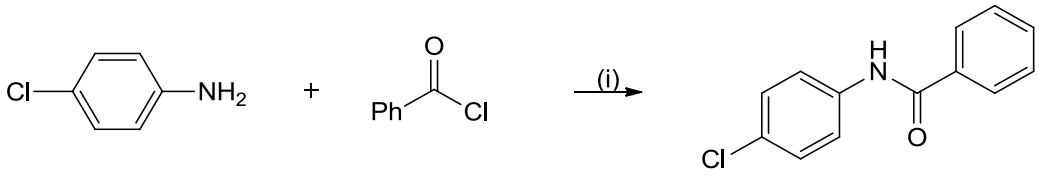
N-(*p*-Chlorophenyl)-benzimidoyl morpholine **353** was synthesised *via* three steps. Preparation of *N*-benzoyl-*p*-chloroaniline **351**, was followed by its conversion to the corresponding imidoyl chloride, *N*-*p*-chlorophenyl-benzimidoyl chloride **352** (Figure 61). Coupling of the crude imidoyl chloride **352** with morpholine yielded the benzamidine *N*-(*p*-chlorophenyl)-benzimidoyl morpholine **353**.



353 **352** **351** **320**

Figure 61: Retrosynthetic analysis for benzamidine 353

N-Benzoyl-*p*-chloroaniline **351** was prepared by a nucleophilic substitution reaction of benzoyl chloride **320** with *p*-chloroaniline **344** (Scheme 171).

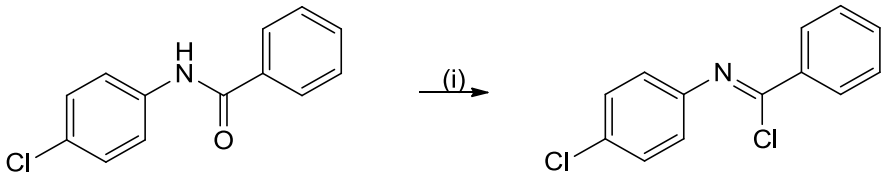


344 **320** **351**

Scheme 171: Reagents: (i) Pyridine, THF

Stirring a solution of the *p*-chloroaniline with benzoyl chloride **351** and pyridine in THF gave the amide in 82% yield following recrystallization with ethanol. Its melting point (190-191.5 ^{o}C) and spectroscopic data correlates well with the literature.[194]

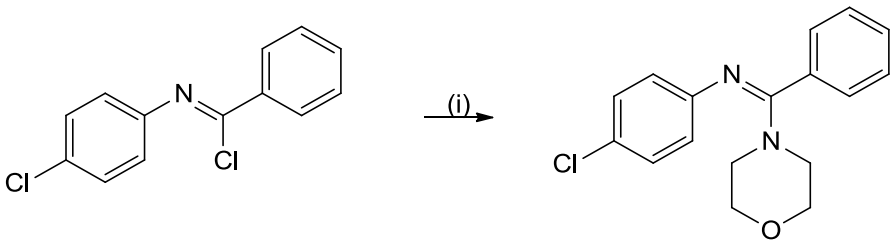
N-*p*-Chlorophenylbenzimidoyl chloride **352** was isolated as a low melting yellow/brown solid following its conversion from the amide **351** with phosphorous pentachloride in toluene (Scheme 172). The imidoyl chloride **352** was used directly in the next step without further purification.



351 **352**

Scheme 172: Reagents: (i) PCl_5, toluene

The benzamidine **353** was generated by combining morpholine with *N*-*p*-chlorophenyl-benzimidoyl chloride **352** in ether (Scheme 173).



352 **353**

Scheme 173: Reagents: (i) Morpholine, ether

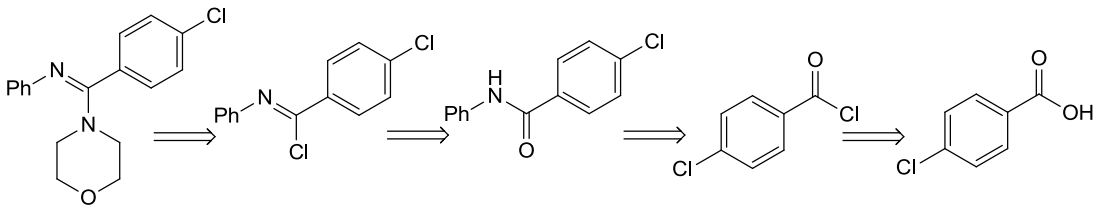
The benzamidine **353** was isolated in 49% yield (over two steps) as a yellow crystalline solid. Its melting point (98-99 ^{o}C) is in the same range as the literature melting point (113.5 °C), but is more than ten degrees lower.[192] Our spectroscopic data for **353** is in accordance with the literature and is outlined in Table 23. The ions of m/z = 301 and m/z = 303 represent the molecular ion species containing the ^{35}Cl and ^{37}Cl isotope respectively.

Table 23: The ^{1}H and ^{13}C NMR spectroscopic data of 353

$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
N(C<u>H</u>$_2$)$_2$	3.41	**N(<u>C</u>H$_2$)$_2$**	46.6
O(C<u>H</u>$_2$)$_2$	3.74	**O(<u>C</u>H$_2$)$_2$**	66.8
Ar<u>H</u> of *p*-substituted Ar	6.47	**5 x Ar<u>C</u>H**	123.9, 128.2, 128.5, 129.0 and 129.0
Ar<u>H</u> of *p*-substituted Ar	6.96	***ipso* <u>C</u> of Ar**	126.4
Ar<u>H</u>	7.09	***ipso* <u>C</u> of Ar**	132.7
Ar<u>H</u>	7.26	**Ar<u>C</u>(Cl)**	149.5
-		**N=<u>C</u>**	161.0

3.3.4 *N*-Phenyl-(*p*-chlorobenzimidoyl)-morpholine

N-Phenyl-(*p*-chlorobenzimidoyl)-morpholine **357** was prepared utilising a four-step synthesis from *p*-chlorobenzoic acid **325** (Figure 62).

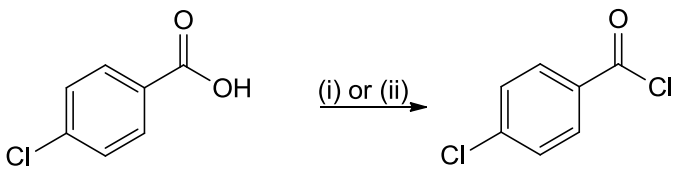


357 **356** **355** **354** **325**

Figure 62: Retrosynthetic analysis of benzamidine 357

3.3.4.1 *p*-Chlorobenzoyl chloride

p-Chlorobenzoic acid was converted into its acid chloride **354** using two different chlorinating agents (Scheme 174). Initially, thionyl chloride was used. *p*-Chlorobenzoyl chloride **354** was isolated in 98% yield as a pale yellow solid. Its formation was confirmed by a peak at 1776 cm^{-1} in its IR spectrum.



325 **354**

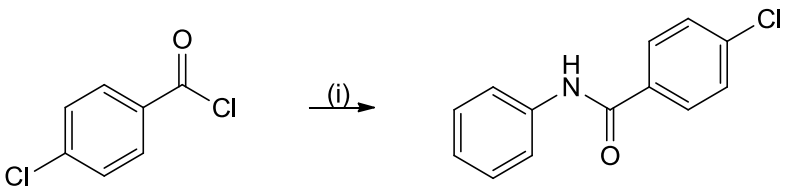
Scheme 174: Reagents: (i) Thionyl chloride, dichloromethane, or (ii) Oxalyl chloride, dichloromethane

The other chlorinating agent employed was oxalyl chloride. IR once again confirmed the formation of the acid chloride by the C=O peak at 1776 cm^{-1}. Oxalyl chloride, while being a

more expensive reagent than thionyl chloride, proved to be much easier to handle. Thionyl chloride is malodorous, is typically used in excess and needs to be removed prior to isolation of the product. Oxalyl chloride on the other hand is used in an equimolar ratio to the acid and the products of the reaction include gaseous carbon monoxide, carbon dioxide and hydrogen chloride.

3.3.4.2 *N*-(*p*-Chlorobenzoyl)-aniline

The amide **355** was synthesised by reacting the acid chloride with aniline in THF in the presence of pyridine (Scheme 175).



354 **355**

Scheme 175: Reagents: (i) Aniline, pyridine, THF

N-(*p*-Chlorobenzoyl)-aniline **355** was isolated in 77% yield as a white crystalline solid following recrystallization from ethanol. Its melting point (198-199 ^{o}C) compares well to the literature.[195] The infrared spectra showed the characteristic absorptions at 3351 and 1653 cm^{-1} for the N-H and C=O groups respectively as reported in the literature. The ^{13}C NMR spectroscopic data correlates well with the literature and the molecular structure itself (Figure 63).

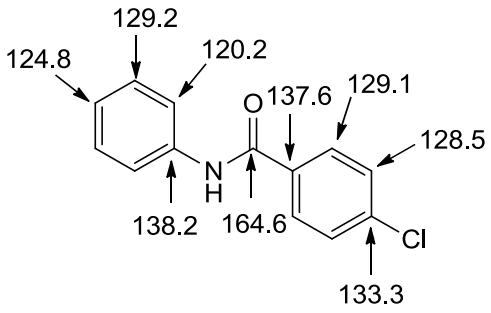
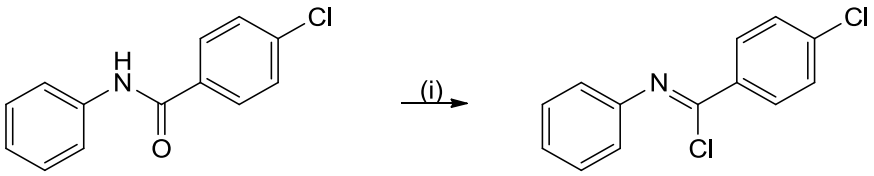


Figure 63: The ^{13}C NMR spectroscopic data of 355

3.3.4.3 *N*-Phenyl-(*p*-chlorobenzimidoyl) chloride

The imidoyl chloride **356** was prepared by heating the amide **355** with phosphorous pentachloride to reflux in toluene (Scheme 176).

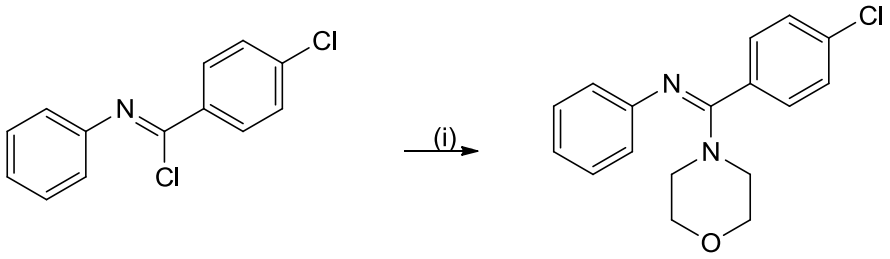


355 **356**

Scheme 176:Reagents: (i) Phosphorous pentachloride, toluene

IR spectroscopy was used to monitor the process and reaction completion was determined by the appearance of the imine stretch (1654 cm^{-1}). The crude product was used directly in the next step without further purification.

The imidoyl chloride **356** was combined with morpholine in the presence of pyridine to give the benzamidine **357** in 52% yield (two steps) as a pale yellow crystalline solid (Scheme 177).



356 **357**

Scheme 177: Reagents: (i) Morpholine, ether

The solid benzamidine **357** melted over a narrow range (138-140 ^{o}C), indicating its purity. Its NMR spectroscopy properties are outlined in Table 24.

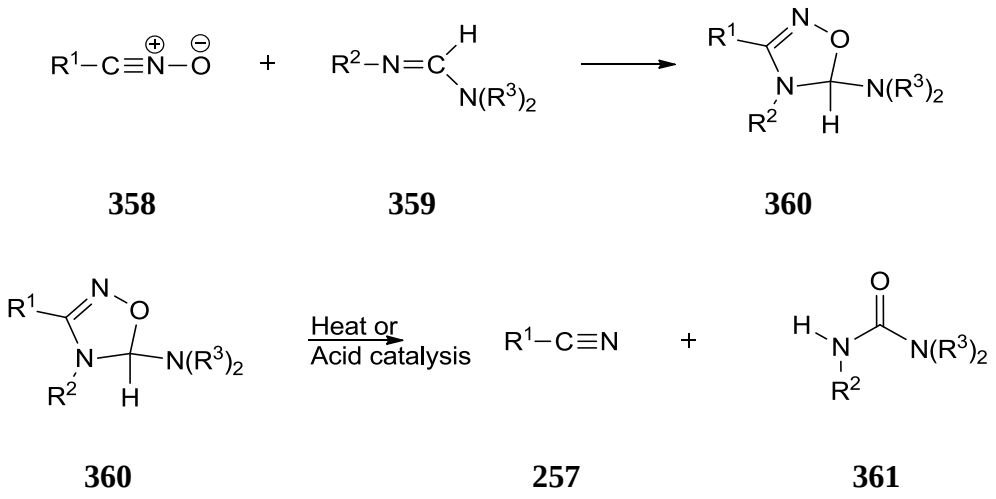
Table 24: The ^{1}H and ^{13}C NMR spectroscopic data of 357

$\delta_{H(ppm)}$			$\delta_{C(ppm)}$	
N(C<u>H</u>$_2$)$_2$	3.38	4H, bs	**N(<u>C</u>H$_2$)$_2$**	46.7
O(C<u>H</u>$_2$)$_2$	3.74	4H, m	**O(<u>C</u>H$_2$)$_2$**	66.8
Ar<u>H</u>	6.53	2H, m	**5 x Ar<u>C</u>H**	121.5, 122.5, 128.4, 128.7, 130.5
***p*-Ar<u>H</u>**	6.78	1H, m	***i*-Ar<u>C</u>**	131.4
Ar<u>H</u>	7.03	4H, m	***i*-Ar<u>C</u>**	134.8
Ar<u>H</u>	7.21	2H, m	**Ar<u>C</u>(Cl)**	150.4
-			**N=<u>C</u>**	159.5

Its molecular ion $[M+H]^{+}$ was observed at m/z = 301 under ESI^{+} conditions. The infrared spectrum showed characteristic absorptions at 3071 (aromatic C-H), 1587 (C=N), 1485 (C-N) and 742 (C-Cl) cm^{-1}.

4 Δ²-1,2,4-Oxadiazolines

We undertook the synthesis of a range of Δ^2-1,2,4-oxadiazolines *via* the 1,3-dipolar cycloaddition of nitrile oxides with amidines (Scheme 178). Previous studies by previous members of this research group investigated the development of a cascade process in which production of a nitrile from a primary nitroalkane was achieved through a heterocyclic intermediate **360** which, without the addition of catalysts or other reactants, would generate the nitrile.[139]



358 **359** **360**

360 **257** **361**

Scheme 178: The 1,3-dipolar cycloaddition reaction of a nitrile oxide and amidine in the formation of a Δ²-1,2,4-oxadiazoline and its subsequent decomposition to the nitrile and urea

It was observed by Creedon, that the rate of nitrile elimination could be accelerated by the presence of electron donating substituents at position -3 and -4 of the five membered ring and by having a nitrogen substituent at position -5 of the heterocycle.[138] The advantages of utilising this cascade-based reaction are numerous-waste is minimised, encourages faster production of the product and would also be less energy consuming. While initial work carried out by Levis illustrated that these heterocyclic intermediates decomposed without heating or acid catalysts producing a nitrile and urea, Hogan sought to capture these heterocyclic intermediates as stable compounds.[140]

Hogan's research investigated the reaction of a series of nitrile oxides with a range of formamidines.[140] Following on from this research base, the nitrile oxides chosen for our study contain electron-withdrawing substituents, which serves to increase the stability of the Δ^2-1,2,4-oxadiazolines formed. Oxadiazolines need to be synthesised as quickly as possible.[138-139] Initially, synthesis included an aqueous work-up (following Hogan's procedure) which gave pure products when the oxadiazoline was stable. However, as the

amidines that we used contained benzyl- groups in place of phenyl group, the oxadiazoline structure was less stable which gave decomposition products rather than the heterocycle. Therefore, time was a factor to be considered when planning the synthetic procedure. Stir time was the first to be reduced. Initial stir times were often 12 h and this was successful in some cases. This lead us to believe that some oxadiazoline preparatory scale reactions could take as little time as ten minutes to execute (including product isolation and ^{1}H NMR spectroscopic analysis).

During our research it was observed, that nitrile oxides appeared to react rapidly with formamidines at room temperature to give Δ^{2}-1,2,4-oxadiazolines. Such was the case that the oxadiazoline was produced within minutes of stirring the nitrile oxide and formamidine at room temperature, thus raising the question, could the reaction rates approach diffusion control?

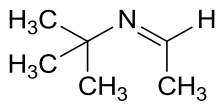
Solvent effects were also explored. Initial methods involved the use of solvents that were immiscible in water. This facilitated the washing out of the triethylamine hydrohalide precipitate which formed when the hydroximoyl halides were dehydrohalogented by the base in generating the nitrile oxide. Dichloromethane, ethyl acetate and ether were used predominantly as solvents which would facilitate an aqueous work-up. Instead of using solvents in this sense, it was concluded that a solvent in which the precipitate was insoluble would be better because it would allow a physical separation of the solid (*via* gravity filtration). Then, simply concentrating the filtrate would produce the oxadiazoline in a pure state.

Stoichiometric equivalents of the nitrile oxide precursor, dipolarophile and base helped in the efficient isolation of the oxadiazoline. [Morrocchi *et al.* used this method of equimolar quantities of nitrile oxide and dipolarophile in their investigations into their reactions of nitrile oxides with arylacetylenes. [27c]] This helped to avoid unnecessary removal of side products, which would ultimately slow down the isolation of the oxadiazoline and may contribute to decomposition processes.

The reported method of addition varies throughout the literature: Martin *et al*. favoured the addition of the base (1.5 equiv) to the hydroximoyl chloride (1.0 equiv.) and excess alkene (either at room temperature or initially at 0 °C and then warm to toom temperature).[64e] However, intially we investigated the addition of hydroximoyl halide to a stirring, cooled solution of the dipolarophile and base. On completion of addition, the solution was warmed to

room temperature and stirred for an amount of time. We felt that this approach would help to reduce the instance of dimerisation of the nitrile oxide to the furoxan. The idea was that the 1,3-dipole would be trapped immediately by the dipolarophile.

Aitken *et al.* outlined different methods for the 1,3-dipolar cycloaddition of nitrile oxides to imines in the formation of Δ^2-1,2,4-oxadiazolines.[196] Firstly, a solution of triethylamine in ether was added dropwise to a cooled (0^o C), stirring solution of the hydroximoyl chloride and imine in ether. The resulting solution was then warmed to room temperature and stirred for 2 h. The solution was then filtered and the solvent evaporated *in vacuo* to yield the product. The second procedure added a solution of the hydroximoyl chloride in ether to a stirring solution of the imine and triethylamine in ether at 0 ^{o}C. The solution was then warmed to room temperature and stirred for 2 h, filtered and evaporated. The former method could be used in the majority of cases, however, in the case of sensitive aliphatic imines such as **362**, the latter method was preferred (Figure 64). Therefore the order of addition was considered important.

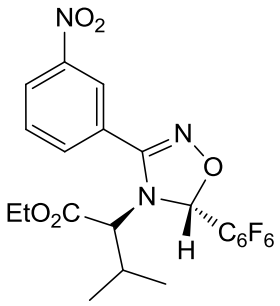


362

Figure 64: Aliphatic imine 362

Torssell *et al.* used solid-phase bases (basic Al_2O_3 and Florisil®) as dehydrohalogenating agents.[28a] They reported that this '*simplified the procedure*' and facilitated the whole sequence of reactions being performed in '*one step*'.

Selecting the correct base to use for dehydrohalogenation of the hydroximoyl chloride is important. Katritzky *et al.* used potassium bicarbonate to neutralise HCl liberated from the hydroximoyl chloride.[24g] Zhu *et al.* explored the use of sodium bicarbonate as well as triethylamine as the dehydrohalogenating agent and reported that sodium bicarbonate reduced the time of reaction from 3 days to 1 day in the synthesis of Δ^2-1,2,4-oxadiazoline **212** (Figure 65).[29] An improved yield as well as facilitating the synthesis of a larger range of oxadiazolines was reported. However, a reduction in enantioselectivity was also noted when triethylamine was used.



212

Figure 65: Δ^2-1,2,4-oxadiazoline 212

Suzuki *et al.* suggest that the '*choice of base*' is '*critical*' especially in the case of *ortho*-disubstituted benzonitrile oxides.[197] Interestingly, 4Å molecular sieves were used as promoters for the reaction i.e. the base for dehydrohalogenation of the chorooxime. The reaction conditions included propan-2-ol as the solvent and a typical reaction temperature of 50 ^{o}C. These conditions were sufficient to generate the *ortho*-disubstituted benzonitrile oxides *in situ* and complete the cycloaddition in 2-60 h.

The temperature of 1,3-dipolar cycloaddition reaction is important as a competing reaction can occur very quickly. Therefore reducing the temperature of the reaction helps to avoid dimerisation of the nitrile oxide.[27e]

The proposed factor contributing to the stability of the Δ^2-1,2,4-oxadiazoline formed through cycloaddition reactions of 1,3-dipoles, from hydroximoyl halide precursors, and amidines is believed to be the electron density by way of lone pair repulsions in the heterocycle. The oxadiazoline structure is made up of a five membered ring containing one oxygen (O_1), two nitrogen (N_2 and N_4) and two carbon (C_3 and C_5) atoms. Each nitrogen atom contributes one pair of lone pair of electrons and the oxygen atom contributes two pairs of lone pairs of electrons. The N_2-O_1 bond (outlined in red in Figure 66) has too much inherent electron density by way of lone pair repulsions which can be relieved by cleavage of that linkage.

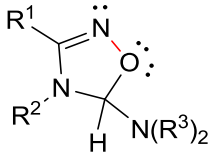
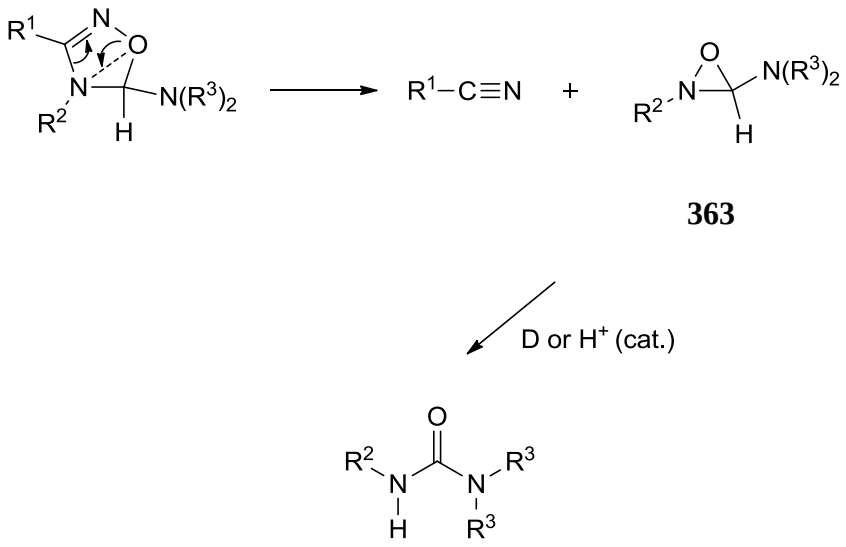


Figure 66: Inherent electron density by way of lone pair repulsions in the Δ^2-1,2,4-oxadiazoline structure

Although the reaction mechanism for thermal, un-catalysed decomposition of the oxadiazoline has not been established, several pathways for this process can be considered.

Initially, putative cyclo-elimination of a nitrile moiety from the oxadiazoline which in turn leads to an amino-oxaziridine intermediate **363** could be explored. Subsequent thermal rearrangement of this species under the reaction conditions employed would lead to formation of the urea (Scheme 179).



Scheme 179: The potential reaction mechanistic pathway to urea from the oxadiazoline

An alternative mechanistic pathway would involve a concerted proton shift, from C_5 to N_4, followed by nitrile elimination (Figure 67). Another possibility could involve a related proton shift to oxygen leading to the generation of an isourea intermediate. The difficulty with this proposal is in identifying a role for the acid catalyst in these mechanisms.

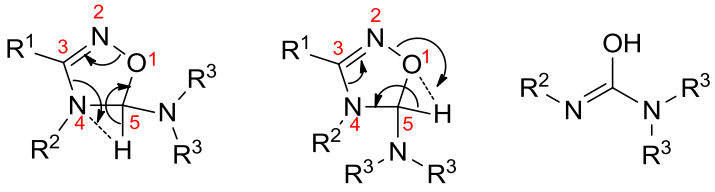
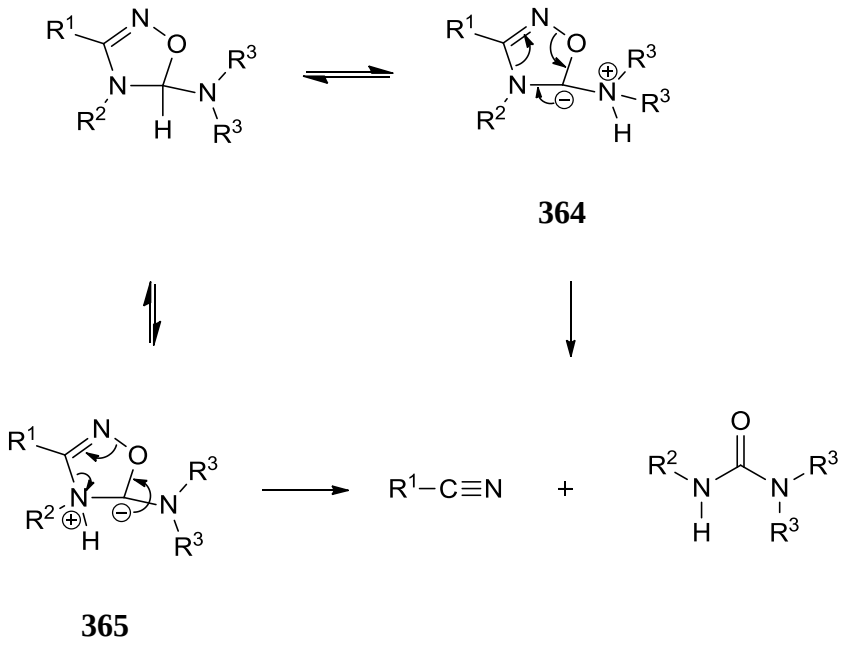


Figure 67: The potential intermediates in the formation of urea

A process involving equilibration of the oxadiazoline with its zwitterion **364** and subsequent elimination of the nitrile from this species cannot be ignored. Neither can a similar route involving zwitterion **365** (Scheme 180).



364

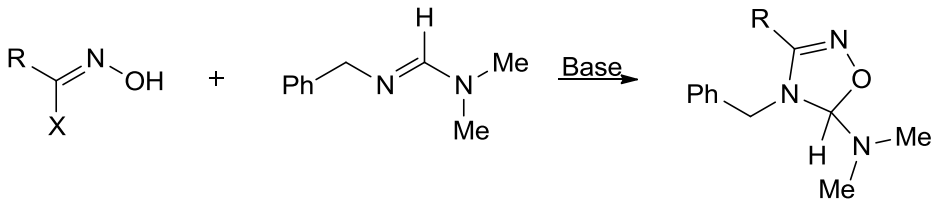
365

Scheme 180: Proposed mechanistic process involving equilibration of the oxadiazoline with its zwitterion 364/365 and subsequent elimination of the nitrile from this species

4.1 1,3-Dipolar cycloaddition reactions with formamidines

4.1.1 Reactions with *N,N*-dimethyl-*N´*-benzylformamidine

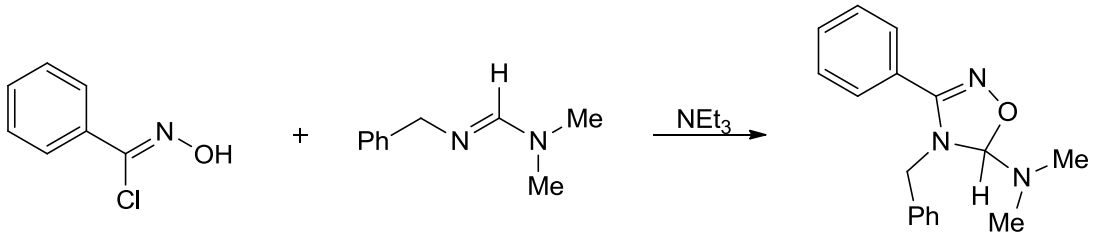
The 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from hydroximoyl halide precursors, with *N,N*-dimethyl-*N´*-benzylformamidine **339** is outlined in the following section. Scheme 181 outlines the 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from substituted benzohydroximoyl halide precursors, with *N,N*-dimethyl-*N´*-benzylformamidine **339**:



339

Scheme 181: The 1,3-dipolar cycloaddition reaction of 1,3-dipoles) with *N,N*-dimethyl-*N´*-benzylformamidine 339

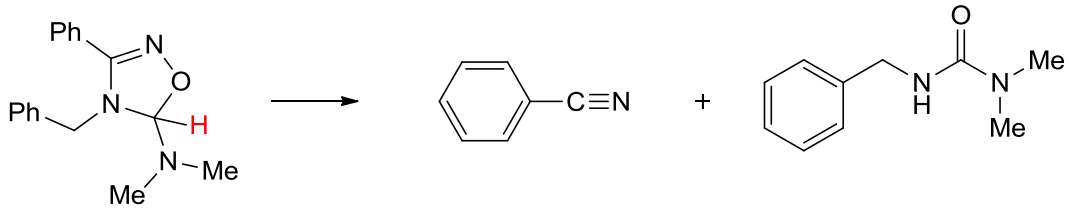
The results of these reactions with a variety of substituted benzohydroximoyl chlorides at an addition temperature of less than 10 °C and triethylamine as the base are summarised in Table 25. Entry 1 (Table 25) illustrates the reaction of benzohydroximoyl chloride **26** with amidine **339** (Scheme 182).



26 **339** **366**

Scheme 182: The 1,3-dipolar cycloaddition reaction of benzohydroximoyl chloride 26 with *N,N*-dimethyl-*N´*-benzylformamidine 339

The benzonitrile **175** and the urea **335** were both observed in the ^{1}H NMR spectrum indicating that the hetereocycle formed and was subsequently converted (Scheme 183). It was impossible to decipher the ratio as there is an overlapping of their characteristic signals in the aromatic region. A ratio of 1:1 would be anticipated as there is not any evidence for the heterocycle **366**. Conclusive evidence for the formation of the oxadiazoline heterocycle would be immediately apparent in the ^{1}H NMR spectroscopic analysis. The proton attached to the C-5 of the oxadiazoline (highlighted in red in oxadiazoline **366** in Scheme 183) is typically observed in the 6 ppm region which integrates as a 1H singlet.

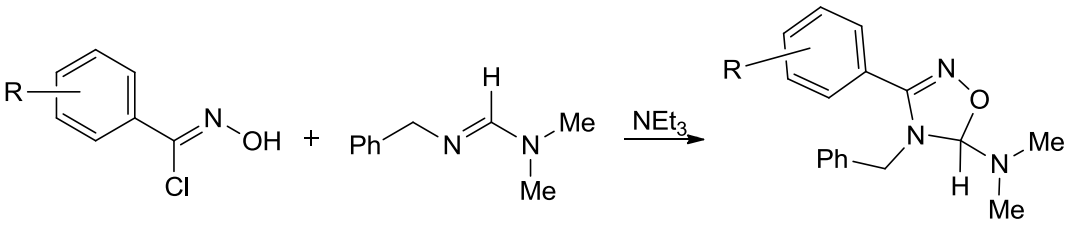


366 **175** **335**

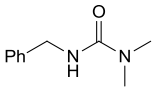
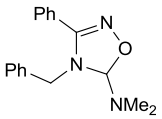
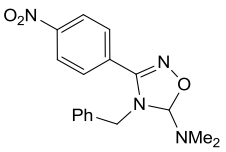
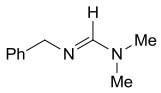
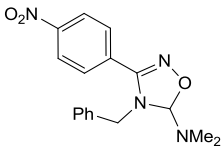
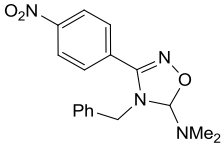
Scheme 183: The conversion of oxadiazoline 366 to nitrile 175 and urea 335

A second attempt at the same conversion (Entry 2) involved a shorter reaction time. The stir time was reduced to 1 h and the triethylamine hydrochloride was isolated by filtration, aiding the rapid isolation of the oxadiazoline **366** in 50% yield. The characteristic proton NMR spectroscopic signal for oxadiazoline formation is of the proton attached to the C5 in the oxadiazoline which is typically in the region of 6ppm. For oxadiazoline **366**, this proton signal was observed at 6.05ppm. This signal coupled to the absence of the precursor peaks (amidine δ_H = 7.38 ppm) indicated that the heterocycle had formed.

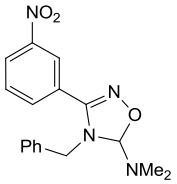
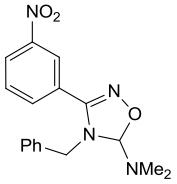
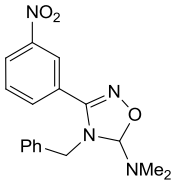
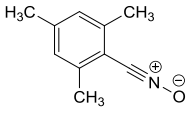
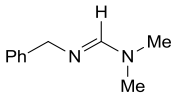
Table 25: 1,3-Dipolar cycloaddition reaction of 1,3-dipoles with *N*,*N*-dimethyl-*N´*-benzylformamidine 339



339

Entry	Precursor	(R)	Solvent	Stir time	Isolation method[2]	Product(s)
1	**26**	H	Ether	12 h	A	**175**  **335**
2	**26**	H	Ether	1 h	B	 **366** 50%
3	**275**	*p*-NO_2	DCM	10 min	A	 **367**  **339** (88:12)
4	**275**	*p*-NO_2-	Ether	1 h	B	 **367** 19%
5	**275**	*p*-NO_2	Ether	10 min	B	 **367** 47%

[2] Method A indicates an aqueous work up, method B indicates isolation by filtration.

Entry	Precursor	(R)	Solvent	Stir time	Isolation method[3]	Product(s)
6	**276**	*m*-NO_2	DCM	10 min	A	 **368**
7	**276**	*m*-NO_2	Ether	1 h	B	 **368** 23%
8	**276**	*m*-NO_2	Ether	10 min	B	 **368** 10%
9	**281**	2,4,6-$(CH_3)_3$	Ether	12 h	A	Unidentified products
10	**281**	2,4,6-$(CH_3)_3$	Ether	10 min	B	 **7**  **339**

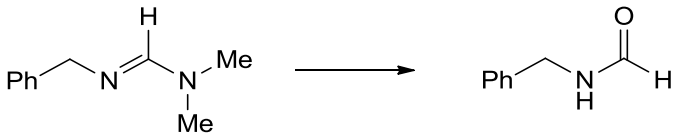
An attempt to introduce thermal stability into the heterocycle by attaching a more electron-withdrawing group (R = *p*-nitrophenyl) is illustrated by entry 3, which shows the production of oxadiazoline **367**. The formation of oxadiazoline **367** was confirmed by the presence of the oxadiazoline proton NMR spectroscopic signal at 6.14 ppm. With a reaction stir time of ten minutes followed by an aqueous work-up, it appears that the reaction did not go to completion. The oxadiazoline **367** and amidine **339** were isolated as a mixture in a ratio of 88 : 12. Entry 4 shows the reaction of the same substrates but with a stir time of one hour. In this case, the cycloaddition reaction went to completion and the oxadiazoline **367** was isolated in 19% yield after recrystallisation as a bright yellow solid. However, the parent molecular ion was not observed during mass spectral analysis. Incorporating a faster isolation time by carrying out a filtration of the triethylamine hydrochloride precipitate in conjunction with a

[3] Method A indicates an aqueous work up, method B indicates isolation by filtration.

ten minute stir time was once again attempted. In this case, the oxadiazoline **367** was successfully isolated as a yellow solid in 47% yield (Entry 5).

We then investigated if the nitro substituent in a *meta*-position of the aromatic ring would influence the reaction outcome. The Hammett σ constants for *m*-nitro (+0.71) and *p*-nitro (+0.78) substituents on phenyl rings are similar so one would predict that the nitrile oxides should react at a similar rate.[52] Entries 6-8 (Table 25) portray the action of *m*-nitrobenzohydroximoyl chloride **276** with the formamidine **339**. Whether a stir time of ten minutes or an hour was employed, the oxadiazoline **368** was isolated, regardless of the purification procedure. However, there was a variation in the yield of oxadiazoline. When the reaction was carried out in dichloromethane (Entry 6), a yield >100% was attributed to dichloromethane present in the sample. Increasing the stir time to one hour resulted in a yield of 23% (Entry 7). The formation of the oxadiazoline **368** was confirmed by the presence of the oxadiazoline proton signal at 6.14 ppm in the ^{1}H NMR spectroscopic analysis.

The results of the reactions of 2,4,6-trimethylbenzohydroximoyl chloride **281** with formamidine **339** is outlined in entries 9-10. The absence of an oxadiazoline peak in the ^{1}H NMR spectrum following overnight stirring suggests that the oxadiazoline did not form. Since the ^{1}H NMR spectrum peaks do not correlate to the amidine **339** or the mesitonitrile-*N*-oxide **7**, the amidine **339** may have hydrolysed to the amide **319** (Scheme 184). Comparison with an authentic sample of amide **319** confirms this.



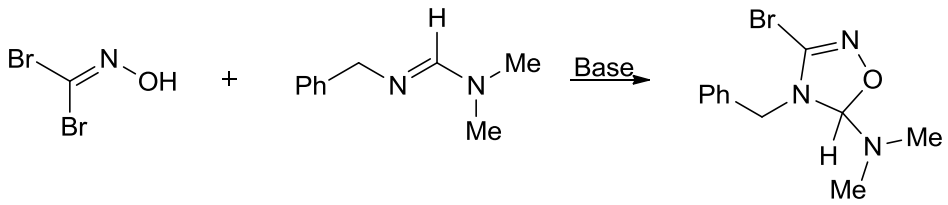
339 **319**

Scheme 184: Hydrolysis of amidine 339 to the amide 319

Entry 10 shows that the cycloaddition did not take place within 10 min as the amidine (δ_H = 7.38 ppm) and nitrile oxide were evident. The dehydrohalogenation did occur as is evident by the formation of mesitonitrile-*N*-oxide **7** which has characteristic proton NMR spectroscopy signals at 2.30 and 2.42 ppm. This suggests that the mesitonitrile-*N*-oxide/amidine **339** combination is not as reactive as that of the amidine with other nitrile oxides.

The 1,3-dipolar cycloaddition reaction of 1,3-dipoles from dihaloformaldoxime precursors with *N,N*-dimethyl-*N´*-benzylformamidine **339** is discussed in this section. To explore the

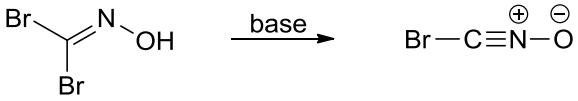
effect of introducing bromine as a substituent at the 3-position of the heterocycle **370**, the reaction of dibromoformaldoxime **41** with formamidine **339** was attempted (Scheme 185).



41 **339** **370**

Scheme 185: The 1,3-dipolar cycloaddition reaction of 1,3-dipoles (from dihaloformaldoxime precursors) with *N*,*N*-dimethyl-*N´*-benzylformamidine 339

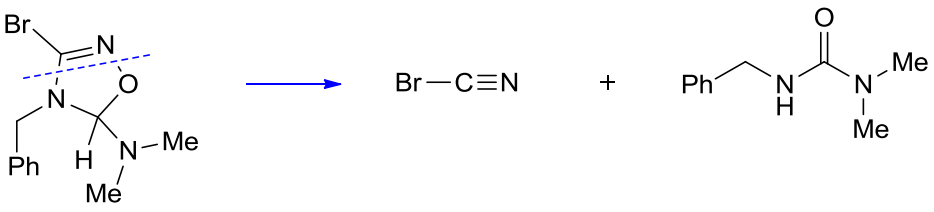
Typically, we used in the dehydrohalogenation of the hydroximoyl halide precursors. However, in the case of dibromoformaldoxime, Herdewijn *et al.*[145f] found that the bromonitrile oxide **13** could not be generated from dibromoformaldoxime **41**, when triethylamine was used as the base (Scheme 186). Therefore potassium *t*-butoxide was used initially to generate the nitrile oxide in the synthesis of oxadiazoline **370**.



41 **13**

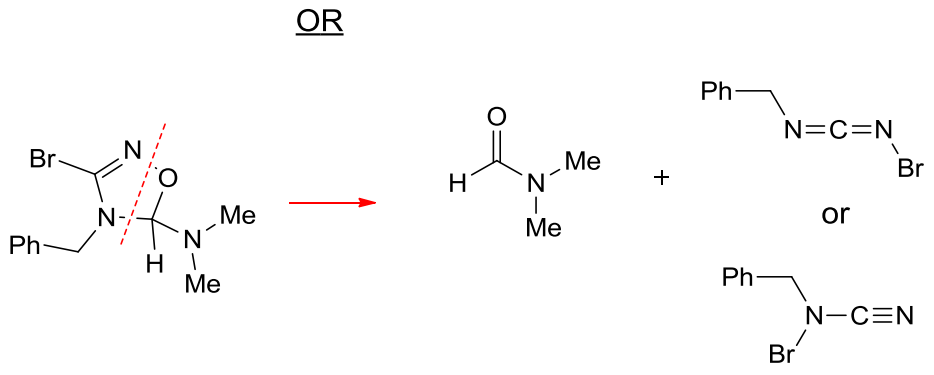
Scheme 186: The conversion of dibromoformaldoxime 41 to bromonitrile oxide 13

The result of this reaction was the formation of *N*,*N*-dimethylformamide **371** and unidentified product(s). This suggests that if the heterocycle formed and then degraded, it may have proceeded to the nitrile (cyanogen bromide **372**) and the urea **335** (Scheme 187) in competition with another process (formation of DMF **371**, Scheme 188). Cyanogen bromide would not be recognisable by ^{1}H NMR spectroscopic analysis but the urea **335** should be identifiable.



370 **372** **335**

Scheme 187: The heterocycle formation and subsequent degradation may have proceeded to the nitrile (cyanogen bromide 372) and the urea 335

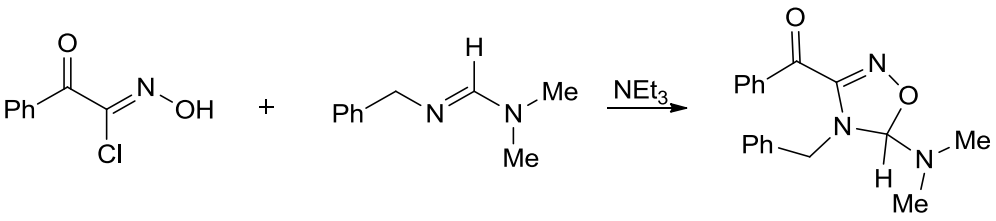


370 **371**

Scheme 188: The proposed competing cycloreversion reaction of oxadiazoline 370

Repeating the reaction with a shorter stir time (10 min) and using triethylamine as the base gave similar results. *N*,*N*-Dimethylformamide **371** was isolated along with unknown product(s).

The 1,3-dipolar cycloaddition reaction of 1,3-dipoles from 1-aroyl-1-chloroformaldoxime precursors with *N*,*N*-dimethyl-*N´*-benzylformamidine **339** involved the reaction of 1-benzoyl-1-chloroformaldoxime **286** with formamidine **339** in the preparation of oxadiazoline **373** (Scheme 189). A one hour stir time combined with isolation of the product by filtration gave the oxadiazoline in 44% yield as a pale yellow oil whose spectroscopic properties were in excellent agreement with the structure.



286 **339** **373**

Scheme 189: The 1,3-dipolar cycloaddition reaction of 1,3-dipoles with *N*,*N*-dimethyl-*N´*-benzylformamidine 339

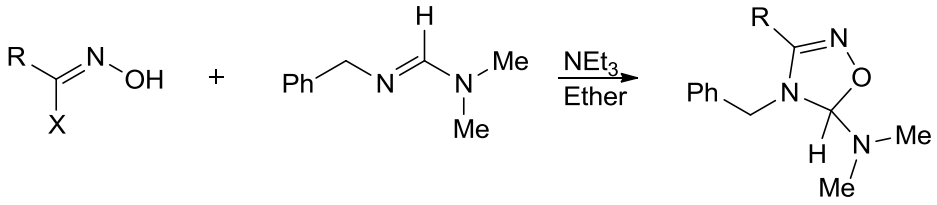
The characteristic ^{1}H NMR spectroscopic signal was identified at 6.12 ppm for the proton attached to the C-5 of the heterocycle (Table 26). The parent molecular ion was not observed in the mass spectral data. However, a methanol adduct of the parent molecular ion ($M+H^{+}+HOMe$) was present at 342 amu under ESI conditions. Isolating the oxadiazoline **373** within 10 min of stirring gave a slight increase in yield to 51%.

Table 26: The ^{1}H and ^{13}C NMR spectroscopic data of 373

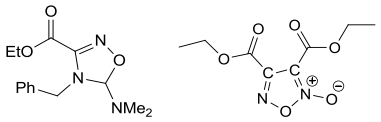
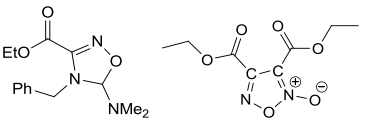
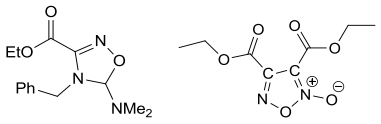
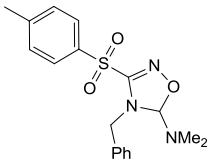
$\delta_{H(ppm)}$		$\delta_{C(ppm)}$	
N(C<u>H</u>$_3$)$_2$	2.38	**N(<u>C</u>H$_3$)$_2$**	36.4
PhC<u>H</u>$_2$	4.29 & 5.08	**Ph<u>C</u>H$_2$**	46.5
NC<u>H</u>ON	6.12	**N<u>C</u>HON**	107.7
Ar<u>H</u>	7.29	**6 x Ar<u>C</u>H**	127.8, 128.4, 128.7, 130.5 & 134.1
***m*-Ar<u>H</u>**	7.46	***ipso* <u>C</u> of Ar**	136.0
***p*-Ar<u>H</u>**	7.60	***ipso* <u>C</u> of Ar**	136.7
***o*-Ar<u>H</u>**	8.12	**<u>C</u>=N**	151.4
-		**<u>C</u>=O**	183.6

Table 27 outlines the 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from other hydroximoyl halide precursors, with *N*,*N*-dimethyl-*N´*-benzylformamidine **339**:

Table 27: The 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from other hydroximoyl halide precursors, with *N*,*N*-dimethyl-*N´*-benzylformamidine 339

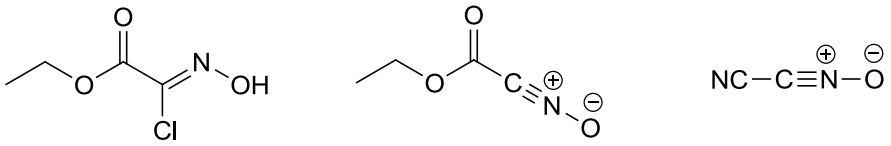


295, 299 **339** **374, 375**

Entry	Precursor	(R)	X	Stir time	Isolation method[4]	Product(s)
1	**295**	EtO_2C-	-Cl	12 h	A	 **374** **315** (85 : 15)
2	**295**	EtO_2C-	-Cl	1 h	B	 **374** **315** (78 : 22)
3	**295**	EtO_2C-	-Cl	10 min	B	 **374** **315** (32 : 68)
4	**299**	Ts-	-Br	10 min	B	 **375** 47%

Disclosures in the literature by Kozikowski *et al.*,[157] emphasise the versatility of ethylchloroglyoxalate oxime as a dipole precursor (Figure 68). '*Due to the ready availability of chlorooxime **295**, we were able to more easily examine the reactivity of **376** with a large number of alkenes. Since **376** generally gave higher yields of cycloadducts than did **304** and since its immediate precursor is more easily prepared, **376** is clearly the dipole of choice*.' [157]

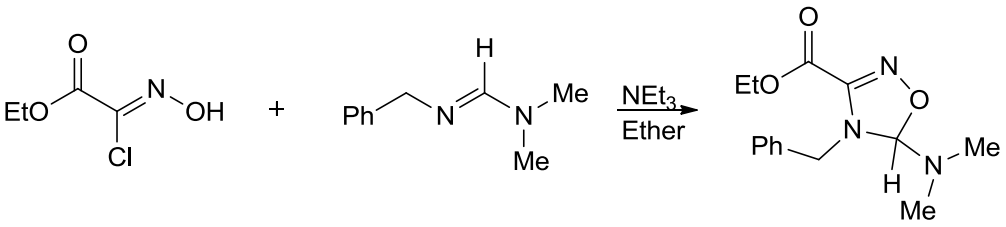
[4] Method A indicates an aqueous work up, method B indicates isolation by filtration.



295 **376** **304**

Figure 68: The structures of nitrile oxides 295, 376 and 304

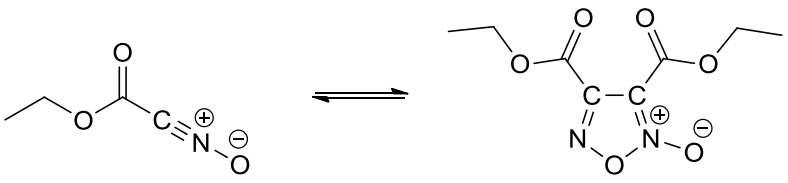
The outcome from our reaction of ethylchloroglyoxalate oxime **295** with the formamidine **339** (Scheme 190) is outlined in Entries 1-3 (Table 27). The oxadiazoline product **374** was isolated as a yellow oil following stirring of the reactants overnight. The ^{1}H NMR spectroscopic analysis of that oil showed the characteristic proton signal for the oxadiazoline was observed at 6.08 ppm as well as the presence (15%) of furoxan **315** as illustrated by the characteristic signals at 1.42 and 4.48 ppm. Reducing the stir time to 1 h and to 10 min respectively showed that oxadiazoline **374** was generated within a shorter reaction time (10 min). However, the quantity of furoxan **315** increased as the reaction time became shorter. The rate of addition of ethyl chloroglyoxalate oxime **295**, although still dropwise, may have been increased during the shorter reaction times, accounting for the increase in furoxan **315** (up to 68%).



295 **339** **374**

Scheme 190: The 1,3-dipolar cycloaddition reaction of ethylchloroglyoxalate oxime 295 with *N*,*N*-dimethyl-*N´*-benzylformamidine 339

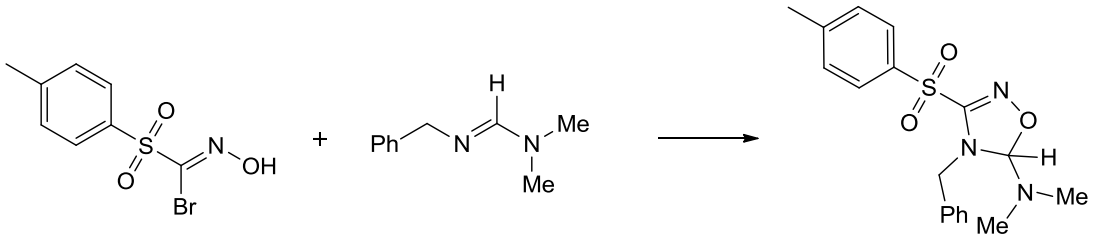
The formation of furoxan **315** during 1,3-dipole generation from the hydroximoyl chloride is well documented in the literature, with a number of experimental techniques being employed to reduce furoxan formation (Scheme 191).[157,198] Dimerisation of the nitrile oxide to the furoxan may be reversible under the reaction conditions used.



376 **315**

Scheme 191: The dimerisation of nitrile oxide 376 to furoxan 315

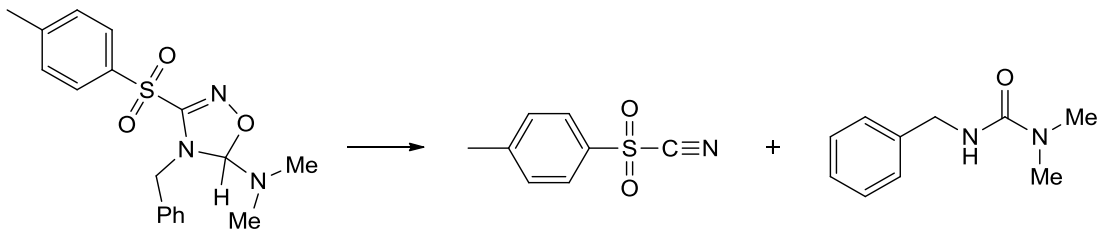
Entry 4 illustrates the reaction of 1-(*p*-toluenesulfonyl)-1-bromoformaldoxime **299** with amidine **339** in the preparation of the oxadiazoline **375** (Scheme 192).



299 **339** **375**

Scheme 192: 1,3-Dipolar cycloaddition reaction of 299 with amidine 339

Comparison of the ^{1}H NMR spectrum of an authentic sample of the urea **335** and literature data of the nitrile **377** indicate that the oxadiazoline **375** had been isolated in a mixture with nitrile **377** and urea **335** (ratio of 66 : 17 : 17) (Scheme 193).[199] The characteristic proton signal for the oxadiazoline was observed at 5.94 ppm indicating the heterocycle had formed.



375 **377** **335**

Scheme 193: The cycloreversion of oxadiazoline 375 to the corresponding nitrile 377 and urea 335

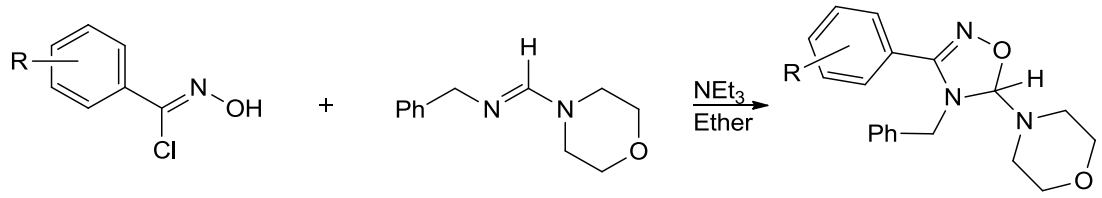
Having the *N*,*N*-dimethylamino group at C-5 position on the oxadiazoline ring inhibits our ability to isolate the corresponding oxadiazolines. This is potentially due to the fact that the Δ^{2}-1,2,4-oxadiazoline is a small heterocycle with three electron density rich heteroatoms-oxygen and nitrogen. The nitrogen on the C-5 of the molecule would also contribute to electron pair repulsion, especially at the N-O of the oxadiazoline, and result in an un-

catalysed decomposition of the oxadiazoline. Electron withdrawing groups would reduce the electron density of the N-O bond through inductive effects and thereby stabilise the structures. In an effort to stabilise the oxadiazoline structure, introduction of a more electron withdrawing morpholine group at C-5 was explored. It was anticipated that the morpholino group would yield isolable oxadiazolines.

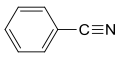
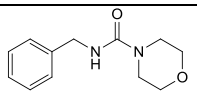
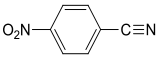
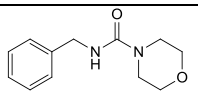
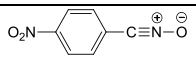
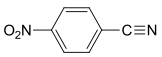
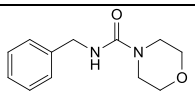
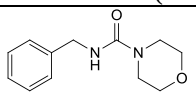
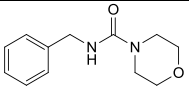
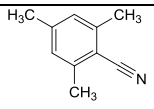
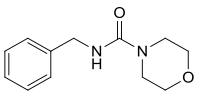
4.1.2 Reactions with *N*-benzylformimidoylmorpholine

A variety of substituted benzohydroximoyl chlorides were reacted with *N*-benzylformimidoylmorpholine **318** at an addition temperature of less than 10 ^{o}C and triethylamine as the base. The results of these reactions are summarised in Table 28.

Table 28: The 1,3-dipolar cycloaddition reaction of 1,3-dipoles with *N*-benzylformimidoylmorpholine 318

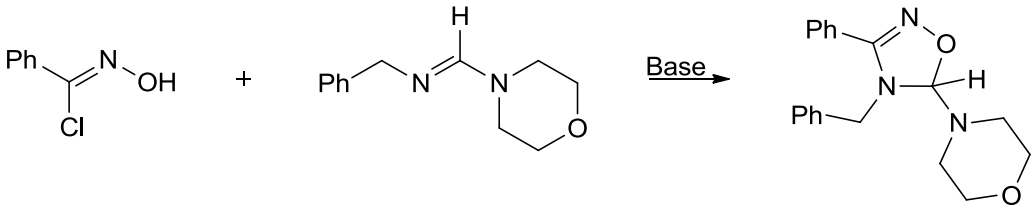


318

Entry	Precursor	(R)	Stir time	Isolation method[5]	Product(s)
1	**26**	H-	12 h	A	 **175**  **336** (1 : 1)
2	**275**	*p*-NO_2-	12 h	A	 **378**  **336** (1 : 1)
3	**275**	*p*-NO_2-	10 min	A	 **265** 6%
4	**275**	*p*-NO_2-	10 min	B	 **378**  **336** (1 : 1)
5	**276**	*m*-NO_2-	10 min	B	 **336** & Unidentified Product(s)
6	**281**	2,4,6-$(CH_3)_3$-	12 h	A	 **336** 0.01%
7	**281**	2,4,6-$(CH_3)_3$-	10 min	B	 **379**  **336** (67 : 33)

[5] Method A indicates an aqueous work up, method B indicates isolation by filtration.

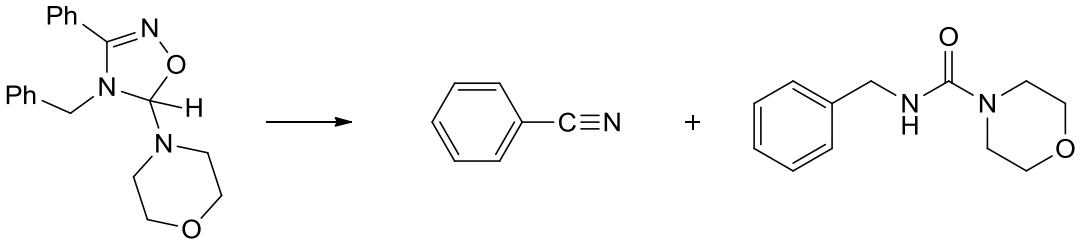
Entry 1 (Table 28) illustrates the reaction of benzohydroximoyl chloride **26** with *N*-benzylformimidoylmorpholine **318** in the attempted synthesis of oxadiazoline **380** (Scheme 194).



26 **318** **380**

Scheme 194: The reaction of benzohydroximoyl chloride 26 with *N*-benzylformimidoylmorpholine 318

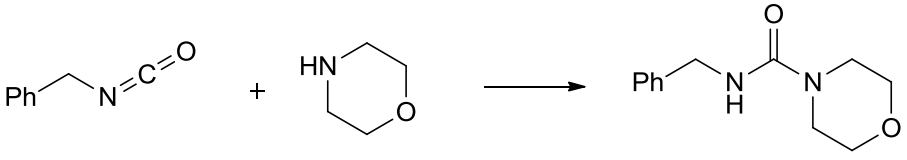
The reagents were stirred overnight and an attempt at isolating the oxadiazoline **380** was made following an aqueous work-up. However, the nitrile **175** and urea **336** were the only products isolated in 42.7% yield and in a 1:1 ratio,indicating that the oxadiazoline **380** had decomposed (Scheme 195).



380 **175** **336**

Scheme 195: The conversion of oxadiazoline 380 to nitrile 175 and urea 336

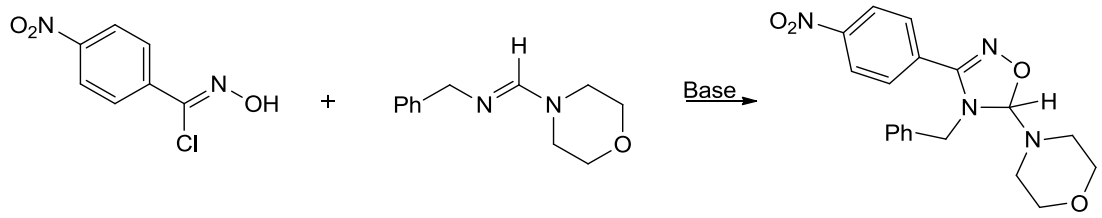
Their presence was confirmed by comparison of the spectroscopic properties of nitrile **175** with literature data and comparison of the urea **336** with an authentic sample of the compound.[200] The authentic sample of urea **336** was produced through the reaction of benzylisocyanate **334** with *N*-morpholine **321** (Scheme 196).



334 **321** **336**

Scheme 196: Reaction of benzylisocyanate 334 with *N*-morpholine 321 to form urea 336

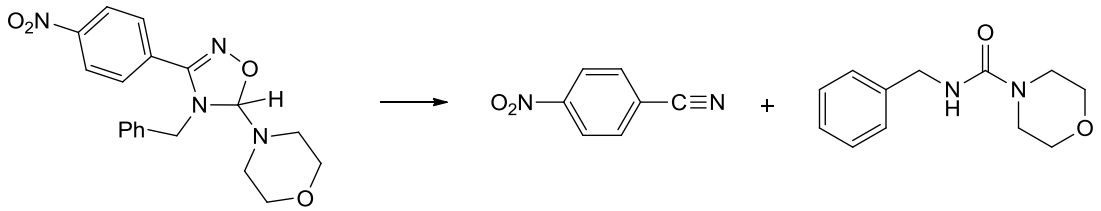
Entries 2-4 chart the results achieved when *p*-nitrobenzohydroximoyl chloride **275** was combined with amidine **318** to prepare a sample of oxadiazoline **381** (Scheme 197). An overnight stir of the reaction mixture was employed.



275 **318** **381**

Scheme 197: The preparation of oxadiazoline 381

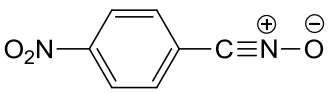
Subsequent analysis of the product mixture showed that it was composed of a small amount of the oxadiazoline **381** combined with the nitrile **378** and urea **336** as the major products. As the oxadiazoline was still present, it can be concluded that the oxadiazoline was in the process of decomposition (Scheme 198). The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.08 ppm as a 1H singlet in ^{1}H NMR spectrum. The urea **336** was isolated by crystallisation and its identity confirmed by comparison with an authentic sample.



381 **378** **336**

Scheme 198: The cycloreversion of oxadiazoline 381 to nitrile 378 and urea 336

The second attempt (Entry 3) at isolating the oxadiazoline involved a ten minute stir time followed by an aqueous work-up. The yellow solid that resulted had the same spectroscopic properties as the nitrile oxide **265** (Figure 69).

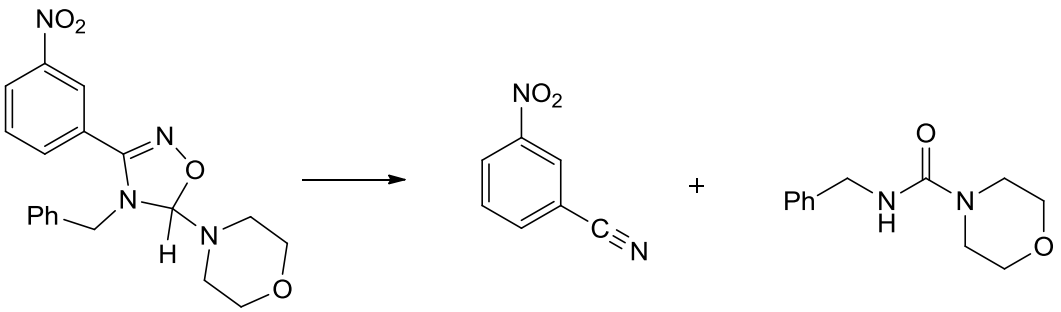


265

Figure 69: The structure of nitrile oxide 265

By introducing filtration of the reaction mixture (Entry 4), it was anticipated that the overall isolation time could be reduced. This resulted in a mixture of compounds being isolated which on comparison with authentic samples of urea **336**, nitrile oxide **265**, hydroximoyl chloride **275** and amidine **318**, illustrated that the urea **336** and nitrile **378** had been isolated. Thus indicating that oxadiazoline **381** had decomposed even in ten minutes.

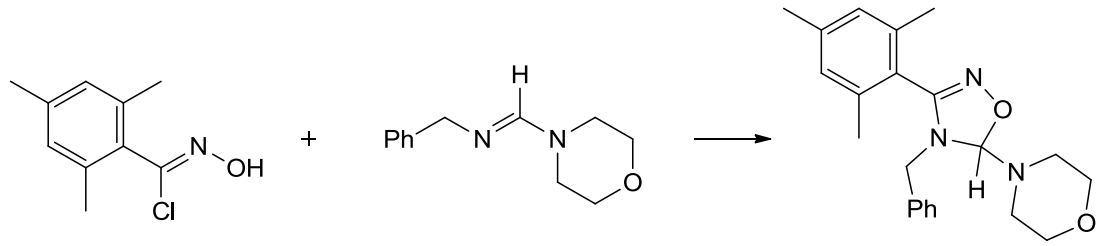
An attempt to insert a *m*-nitrophenyl substituent at the C-3 position of the oxadiazoline (R^1 = *m*-$NO_2C_6H_4$) is illustrated in entry 5 of Table 28. Entry 5 shows a mixture of products with the urea **336** alone being identifiable on comparison with literature data and authentic samples (Scheme 199). The IR spectra show that decomposition had occurred with an intense peak at 3278 cm^{-1} indicating the NH stretch of the urea. This absorption plus an intense peak at 1660 cm^{-1} identifies the urea. The products were poorly soluble in $CDCl_3$ which may have contributed to our difficulty in assigning their molecular structures.



382 **383** **336**

Scheme 199: The conversion of oxadiazoline 382 to nitrile 383 and urea 318.

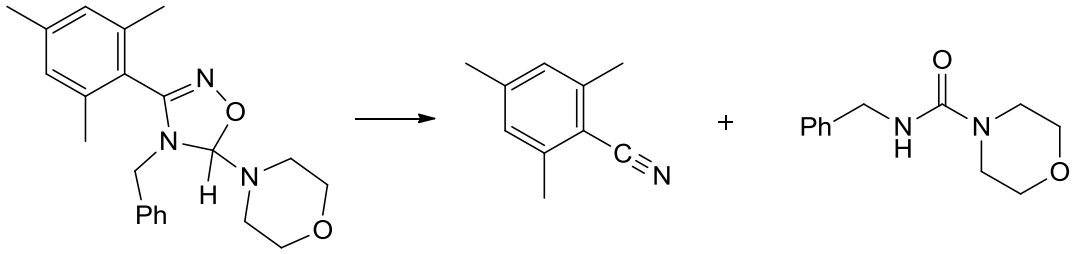
Entry 6 refers to the reaction of 2,4,6-trimethylbenzohydroximoyl chloride **281** with amidine **318** in the attempted synthesis of oxadiazoline **384** (Scheme 200). The reaction mixture was stirred overnight and following recrystallization from ethyl acetate and hexane, the urea **336** was isolated in 0.01% yield.



281 **318** **384**

Scheme 200: The attempted synthesis of oxadiazoline 384

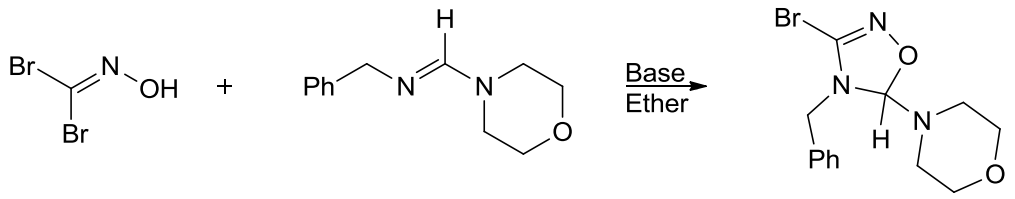
Reducing the stir time to ten minutes and comparing the spectra with the literature data for the nitrile **379** and with an authentic sample of the urea **336** established that a mixture of urea and nitrile was formed in a ratio of 33 : 66 (Entry 7) (Scheme 201).[201] The IR spectrum shows a broad peak at 3296 cm^{-1} and an intense peak at 1671 cm^{-1} which are indicative of urea. The peak at 2291 cm^{-1} could indicate a nitrile group, but is different from that reported by Ushijima *et al*. (2218 cm^{-1}) for 2,4,6-trimethylbenzonitrile **379**. This discrepancy may be due to a different media employed in analysis. Ushijima *et al.* did not specify the media used for their measurements.



384 **379** **336**

Scheme 201: The decomposition of oxadiazoline 384 to nitrile 379 and urea 336

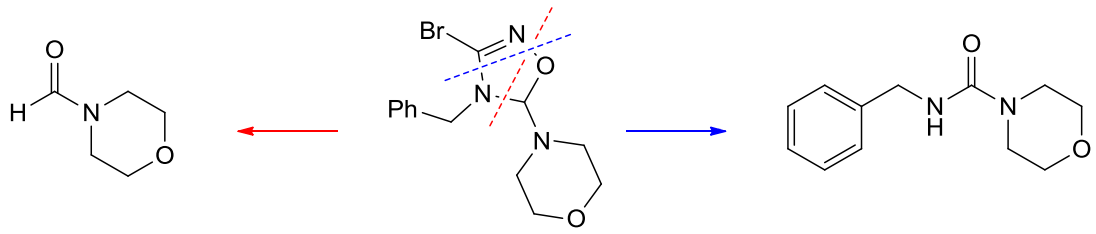
The results of the attempted 1,3-dipolar cycloaddition reactions of 1,3-dipoles from dibromoformaldoxime precursor with *N*-benzyformimidoylmorpholine **318** at an addition temperature of less than 10 ^{o}C is discussed in this section. The reaction of dibromoformaldoxime **41** with amidine **318** which would potentially generate oxadiazoline **385** is outlined Scheme 202. Both experiments were carried out under similar reaction conditions. Different bases were used for dehydrohalogenation - triethylamine and potassium *t*-butoxide - both produced the same outcome.



41 **318** **385**

Scheme 202: The 1,3-dipolar cycloaddition reaction of 41 with *N*-benzylformimidoylmorpholine 318

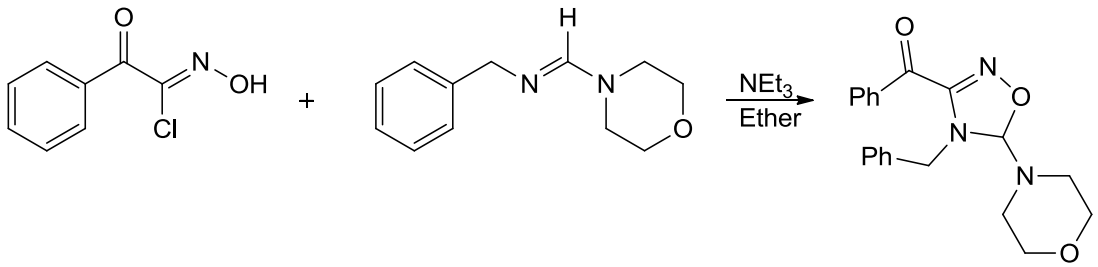
Comparing the reaction mixture with authentic samples of *N*-formylmorpholine **340** and urea **336** showed that both compounds were isolated in a ratio of 50 : 50. This result suggests that the oxadiazoline is decomposing *via* two different pathways simultaneously (Scheme 203). Infrared spectra of the products of both reactions show a peak at ~2216 cm^{-1} which may additionally indicate the presence of a nitrile containing compound.



340 **385** **336**

Scheme 203: The cycloreversion of oxadiazoline 385 *via* two different routes

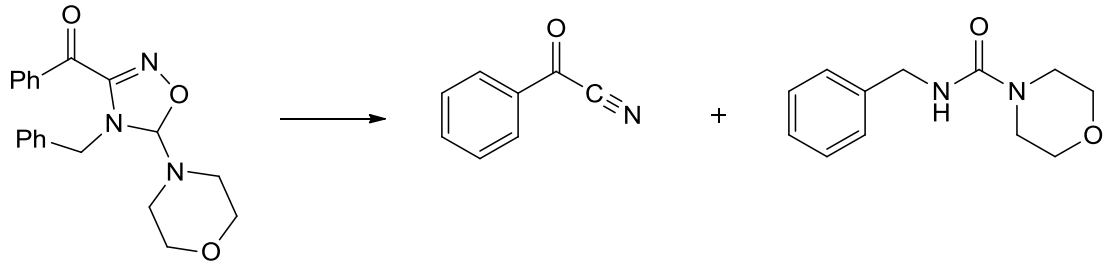
The attempted 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from a 1-aroyl-1-chloroformaldoxime precursor, with *N*-benzylformimidoylmorpholine **318** at an addition temperature of <10 ^{o}C to form oxadiazoline **386** is discussed in this section. Scheme 204 refers to the reaction of 1-benzoyl-1-chloroformaldoxime **286** with amidine **318** in the attempted preparation of oxadiazoline **386**.



286 **318** **386**

Scheme 204: The 1,3-dipolar cycloaddition reaction of 1-benzoyl-1-chloroformaldoxime 286 with *N*-benzylformimidoylmorpholine 318

Comparison of ^{1}H NMR spectrum with an authentic sample of urea **336** and with literature data of nitrile **387** show that both compounds were isolated as a mixture, indicating the oxadiazoline **386** had formed but decomposed (Scheme 205).[202]



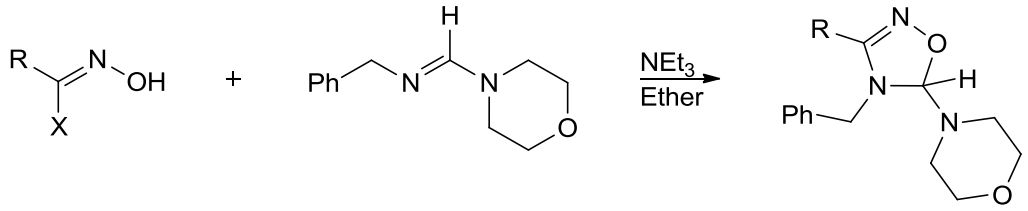
386 **387** **336**

Scheme 205: The cycloreversion of oxadiazoline 386 to form nitrile 387 and urea 336

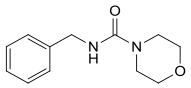
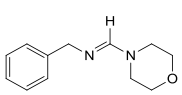
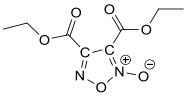
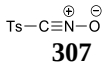
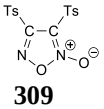
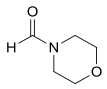
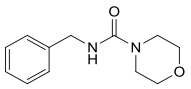
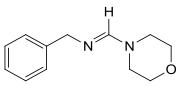
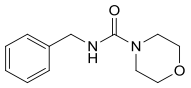
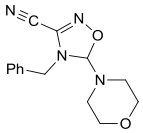
The ratio of products was difficult to determine as the characteristic proton NMR spectroscopy peaks were overlapping. The IR data confirms the presence of a nitrile (2285 cm^{-1}), however this does not correlate closely with the literature data for the compound **387** (2230 cm^{-1}). The discrepancy between the reference data may be the media used to analyse the IR spectrum. A KBr disc was used by Ibrahim *et al.*, whereas we employed a film for IR analysis.[202] The broad absorption at 3285 cm^{-1} shows the presence of the NH of the urea. This combined with the intense peak at 1660 cm^{-1} confirms that secondary conversion of the oxadiazoline into nitrile **387** and urea **336** took place within the ten minute reaction time.

The 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from other hydroximoyl halide precursors, with *N*-benzylformimidoylmorpholine **318** at an addition temperature of <10 °C is outlined in Table 29.

Table 29: The 1,3-dipolar cycloaddition reaction of 1,3-dipoles with *N*-benzylformimidoylmorpholine 318



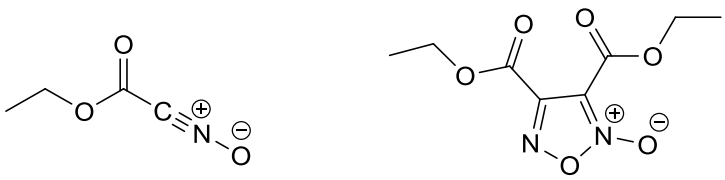
295,299,304 **318** **388,389,390**

Entry	Precursor	(R)	X	Stir time	Isolation method[6]	Product(s)
1	**295**	EtO_2C-	Cl-	12 h	A	 **336** 24%
2	**295**	EtO_2C-	Cl-	10 min	B	 **318**  **315** (43 : 57)
3	**299**	Ts-	Br-	10 min	B	 **307**  **309**  **340**  **336**
4	**304**	NC-	Cl-	30 min	A	 **318**  **336**  **390**

Ethylchloroglyoxalate oxime **295** and amidine **318** were combined to explore potential to prepare oxadiazoline **388** (Entries 1-2, Table 29). An overnight stir time (Entry 1), followed by recrystallization from ethyl acetate and hexane gave no significant amount of any product other than a few crystals of urea **336** (0.01%). Decreasing the stir time to ten minutes (Entry 2) gave a mixture of products. Comparison of ^{1}H NMR spectrum with authentic samples

[6] Method A indicates an aqueous work up, method B indicates isolation by filtration.

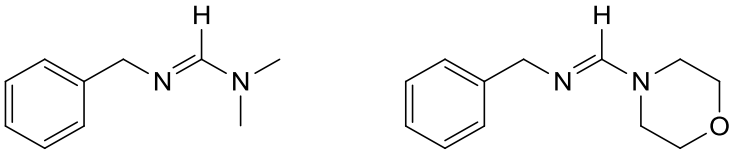
established that *N*-benzylformimidoylmorpholine **318** and 3,4-diethoxycarbonylfuroxan **315** were present in a ratio of 43 : 57. Filtration of the sample should have removed all of the triethylammonium chloride, but it was evident in the ^{1}H NMR spectrum. The complete consumption of triethylamine and the absence of hydroximoyl chloride peaks in the ^{1}H NMR spectrum indicate that the hydroximoyl chloride had been successfully converted to the nitrile oxide **376** (Figure 70). This nitrile oxide is prone to dimerisation and converted into the furoxan before undergoing cycloaddition. Dimerisation of nitrile oxide to **315** is noted in the literature in preference to cycloaddition with slow reacting dipolarophiles.[203]



376 **315**

Figure 70: Nitrile oxide 376 and furoxan 315

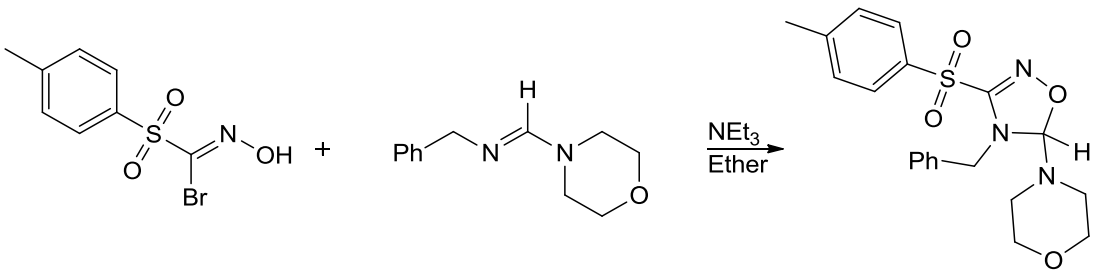
This indicates that the amidine **318** may not be as reactive a dipolarophile as amidine **339** for example, as results outlined in Table 27 illustrates that nitrile oxide **376** did not have the same dimerisation issue when reacted with amidine **339** (Figure 71). Many experimental techniques are outlined in the literature as a means to reduce dimerisation of the nitrile oxide during the cycloaddition reaction. Some involve using a different base, others include physically adding the hydroximoyl chloride as slowly as possible to the base and dipolarophile solution.[157,198]



339 **318**

Figure 71: Amidines 339 and 318

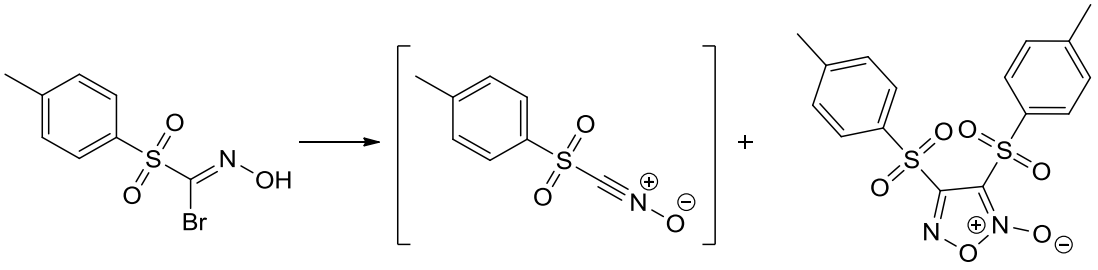
Entry 3 (Table 29) relates to the reaction of 1-*p*-toluenesulfonyl-1-bromoformaldoxime **299** with amidine **318** in the attempted formation of the oxadiazoline **389** (Scheme 206).



299 **318** **389**

Scheme 206: The attempted formation of oxadiazoline 389

With a stir time of ten minutes and the comparison of ^{1}H NMR spectrum with those of authentic samples of urea **336**, nitrile oxide **307**, nitrile oxide dimer **309** and with the literature data of nitrile **377**, indicated that a mixture of products was isolated (Scheme 207).[199]

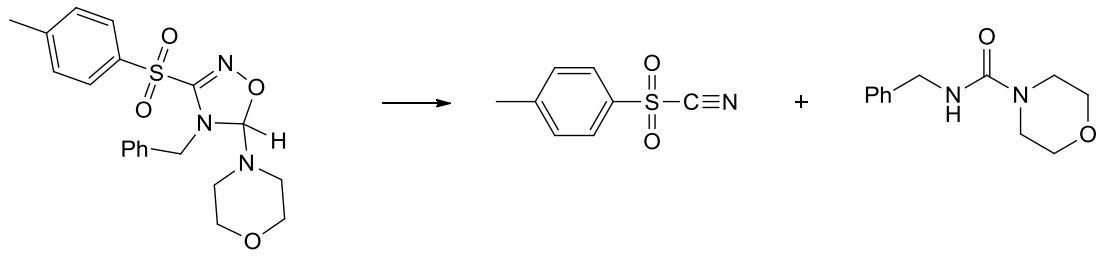


299 **307** **309**

Scheme 207: The dehydrohalogenation of 299

This suggests that while the nitrile oxide **307** dimerised, the oxadiazoline **389** formed but decomposed to the nitrile **377** and urea **336** (Scheme 208). The infrared spectra showed peaks at 3285 and 1655 cm^{-1} which may correlate to the urea **336** and the peak at 2219 cm^{-1} to the nitrile **377**. However, the literature data suggests that the IR absorption for C≡N in compound **377** is 2194 cm^{-1} (film)[7]. The characteristic proton NMR spectroscopic signal for oxadiazoline formation is of the proton attached to the C5 in the oxadiazoline which is typically in the region of 6ppm. For oxadiazoline **389**, this proton signal was observed at 5.94 ppm.

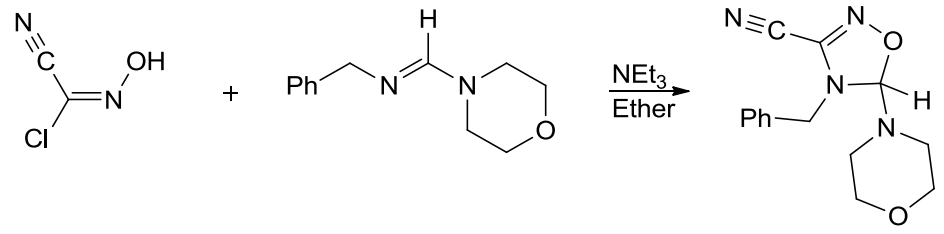
[7] The difference may be attributed to medium effects in the composition of the mixture examined.



389 **377** **336**

Scheme 208: The cycloreversion of oxadiazoline 389 to nitrile 377 and urea 336

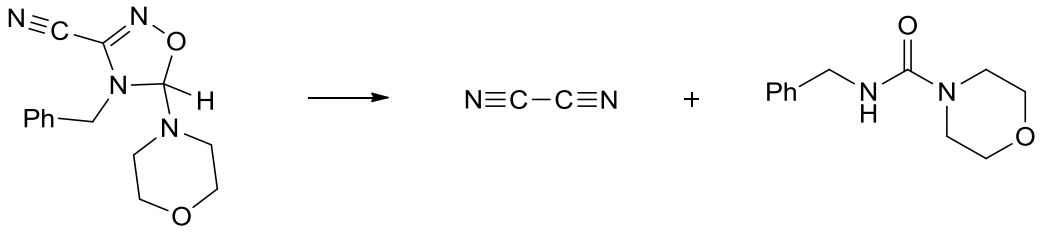
The reaction of cyanoformohydroximoyl chloride **304** with amidine **318** is outlined in entry 4 (Scheme 209). Following a 30 min stir time and an aqueous work-up, a mixture of products was isolated.



304 **318** **390**

Scheme 209: The synthesis of oxadiazoline 390

Spectroscopic comparison with authentic samples of amidine **318** and urea **336** established that both were present (Scheme 210). The oxadiazoline **390** was also present as confirmed by a ^{1}H NMR spectroscopy characteristic singlet at 6.08 ppm. Carbon-13 NMR spectroscopy confirmed the presence of a nitrile at 107.40 ppm indicating cyanogen **391** (NC-CN) was present. It can be concluded that the oxadiazoline **390** was undergoing cycloreversion to the nitrile **391** and urea **336** at the time of analysis.



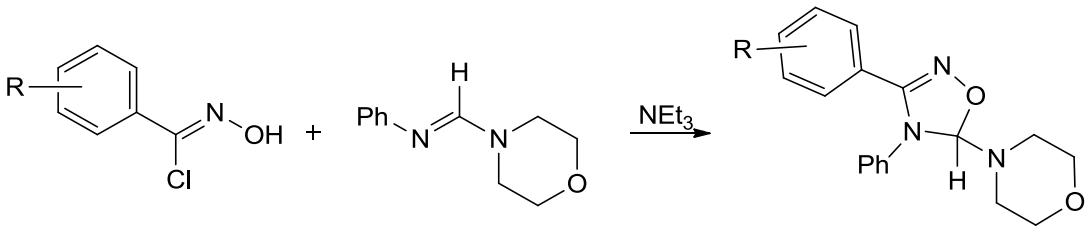
390 **391** **336**

Scheme 210: The cycloreversion of oxadiazoline 390 to the nitrile 391 and urea 336

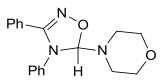
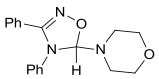
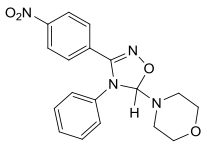
4.1.3 Reactions with *N*-phenylformimidoylmorpholine

In order to promote formation of a more stable oxadiazoline, we changed from an *N*-benzyl to an *N*-phenyl amidine. It was anticipated that the addition of a phenyl substituent directly attached to the oxadiazoline ring at the N-4 position would further stabilise the oxadiazoline formed during the cycloaddition reactions through inductive effects of the aromatic ring. The results of these reactions with a variety of substituted benzohydroximoyl chlorides with *N*-phenylformimidoylmorpholine **341** at an addition temperature of less than 10 ^{o}C and triethylamine as the base are summarised in Table 30.

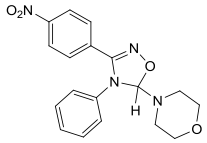
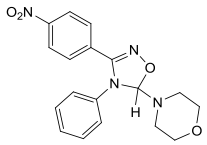
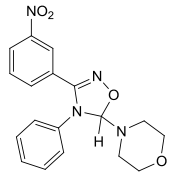
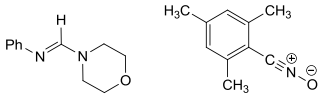
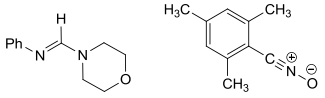
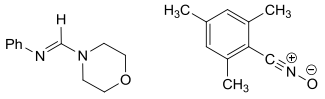
Table 30: The 1,3-dipolar cycloaddition reactions of substituted benzohydroximoyl chlorides with 341



341

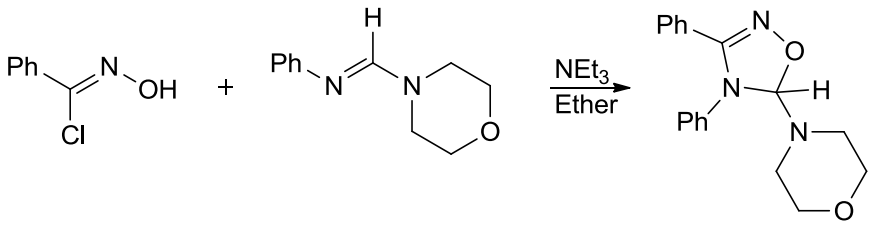
Entry	Precursor	(R)	Solvent	Stir time	Isolation method[8]	Product(s)
1	**26**	H-	Ether	10 min	A	 **267** 26%
2	**26**	H-	Ether	1 h	B	 **267** & Unidentified Products
3	**275**	*p*-NO_2-	Ether	1.25 h	A	 **392** 41%

[8] Method A indicates an aqueous work up, method B indicates isolation by filtration.

Entry	Precursor	(R)	Solvent	Stir time	Isolation method[9]	Product(s)
4	**275**	*p*-NO_2-	Ether	10 min	A	 **392** 29%
5	**275**	*p*-NO_2-	Ether	1 h	B	 **392** 22%
6	**276**	*m*-NO_2-	Ether	1 h	B	 **393** 59%
7	**281**	2,4,6-$(CH_3)_3$-	DCM	1 h @ <10 °C	A	 **341** **7** (50 : 50)
8	**281**	2,4,6-$(CH_3)_3$-	Ether	1 h	B	 **341** **7** (50 : 50)
9[10]	**281**	2,4,6-$(CH_3)_3$-	DCM	12 h	A	 **341** **7** (50 : 50)

Entries 1-2 show the reaction of benzohydroximoyl chloride **26** with amidine **341** in the preparation of oxadiazoline **267** (Scheme 211). With a ten minute stir time (Entry 1), an aqueous work-up and recrystallization from ethyl acetate and hexane, the oxadiazoline was isolated as a white solid in 26% yield. The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.13 ppm as a 1H singlet in its ^{1}H NMR spectrum.

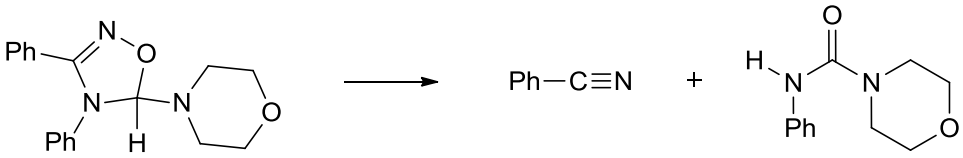
[9]Method A indicates an aqueous work up, method B indicates isolation by filtration.
[10]Addition temperature increased to 20°C for this entry.



26 **341** **267**

Scheme 211: The synthesis of oxadiazoline 267

A study of the conversion of the oxadiazoline **267** into its nitrile **175** and urea **395** products (Scheme 212) by time course ^{1}H NMR spectroscopic analysis was next undertaken.



267 **175** **395**

Scheme 212: The conversion of oxadiazoline 267 to nitrile 175 and urea 395

Figure 72 illustrates that the urea **395** began to form within 24 h of storing the oxadiazoline **267** in chloroform-d_1 at room temperature. Subsequent analysis showed that the oxadiazoline **267** remained in a small quantity after 46 days at 300 K.

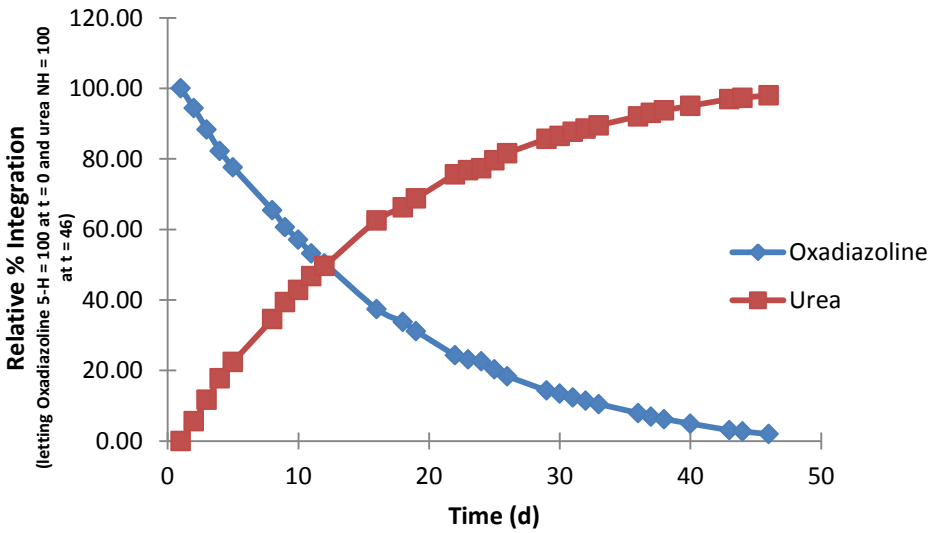
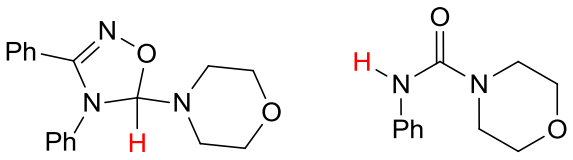


Figure 72: The conversion of oxadiazoline 267 to urea 395 in $CDCl_3$ at 300 K (Scheme 212)[11]

[11] All experimental data and calculations used in the plotting of graphs in this section is outlined in Table 44.

To explore the rate of conversion of the oxadiazoline into urea, proton NMR spectroscopic analysis was the tool used. To determine the relative concentration of oxadiazoline and urea in the sample analysed, the relative integral of the heterocyclic 5-H proton in oxadiazoline **267** was integrated as being equivalent to one proton in each proton NMR spectrum obtained over the time course of this study. The relative integral of the urea NH proton was then determined in comparison to the oxadiazoline 5-H proton signal in the same spectrum (Figure 73). These values were combined to give the overall total integration. The concentration of oxadiazoline, relative to that at t = 0 days, $[\text{oxadiazoline}]_{rel}$ was determined as a percentage of the oxadiazoline integration divided by the total integration to facilitate the relative rate constant determination. The concentration of urea, relative to that at t = 0 days, $[\text{urea}]_{rel}$ was then determined as a percentage of the urea integration divided by the total integration. For determination of a relative rate constant, k_{rel}, the molar concentration was not used, instead the relative concentrations, as defined by the relative percent integration of the oxadiazoline and urea, denoted $[\text{oxadiazoline}]_{rel}$ and $[\text{urea}]_{rel}$ in the following discussion.



267 **395**

Figure 73: The proton heterocyclic 5-H proton of 267 and the NH proton of 395 (highlighted in red in each structure) used in the determination of concentration for relative rate constant calculation

The rate law for a first order process is given by the expression shown below, where [A] is the molar concentration of the reactant.

$$Rate = k[A]$$

When integrated, the rate law has the following form:

$$\ln[A] = -kt + \ln[A]_0$$

$[A]_0$ is the reactant concentration at t = 0. This equation is in the form of a standard equation of a line, with ln[A] on the *y*-axis, the time in seconds *t* on the *x*-axis, and $\ln[A]_0$ as the intercept. The rate constant *k* can thus be determined from the slope of a plot of:

$$\ln[A] \text{ vs. } t$$

The rate law for a second order process where one reactant is used and is given by the expression shown below, where [A] is the molar concentration of the reactant.

$$Rate = k[A]^2$$

When integrated, the rate law has the following form:

$$\frac{1}{[A]} = \frac{1}{[A]_0} + kt$$

This equation is in the form of a standard equation of a line, with 1/[A] on the *y*-axis, the time in seconds *t* on the *x*-axis, and $1/[A]_0$ as the intercept. The rate constant *k* can thus be determined from the slope of a plot of:

$$\frac{1}{[A]} \text{ vs. } t$$

The oxadiazoline reaction (Table 30, Entry 1) follows first order kinetics, and a relative rate constant (k_{rel} = 9 x 10^{-7} s^{-1}) was calculated from the graph of ln[Oxadiazoline **267**]$_{rel}$ *versus* time (d) (Figure 74).

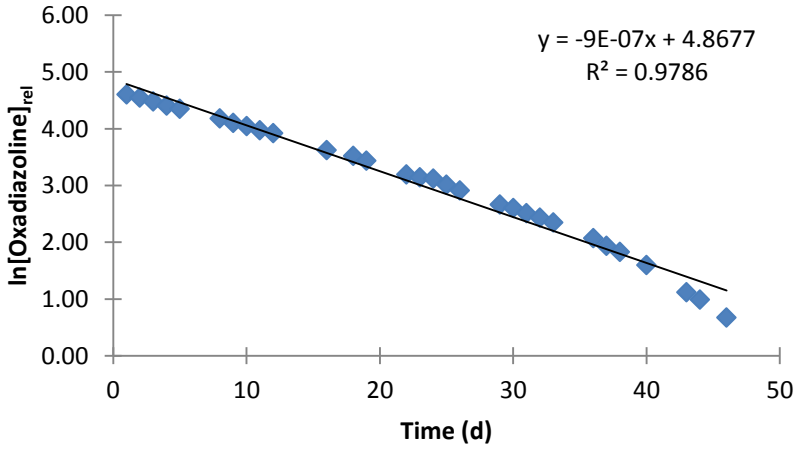


Figure 74: Determination of relative rate constant, k_{rel} by plotting ln[oxadiazoline]$_{rel}$ *vs* time (d) with a straight line fit

Plotting the relative oxadiazoline (Figure 74) and urea (Figure 75) concentrations with time illustrates that each exhibits slightly differing behaviour. The plot of relative oxadiazoline concentration with time portrays a much better correlation to a first order reaction, whereas the plot of relative urea concentration with time shows a biphasic property with a first-order

segment later in the process. This difference may be attributed to the practicality of measuring a signal that disappears with time (the oxadiazoline), which is usually easier, in contrast to the ability to accurately integrate the broad signal of the amide NH that increases with time. However, both of the relative rate constants that were determined are of the same order of magnitude.

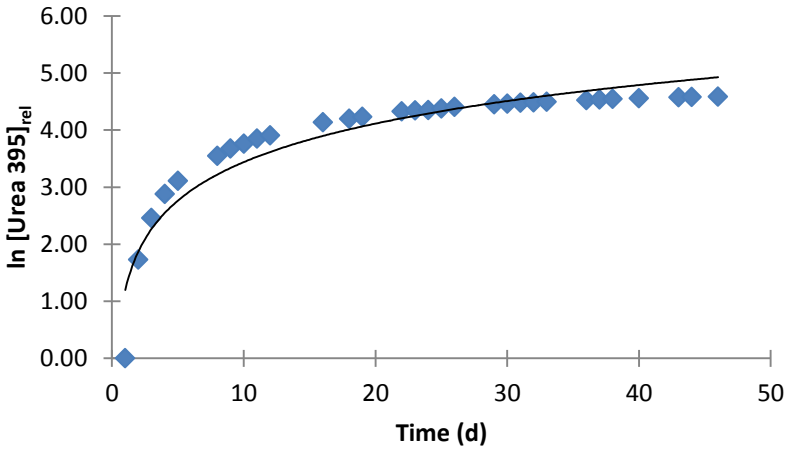


Figure 75: Determination of relative rate constant, k_{rel} by plotting ln[urea 395]$_{rel}$ *vs* time (d) with curve fit

A second order plot does not give a linear correlation for either the oxadiazoline or urea (Figure 76 and Figure 77).

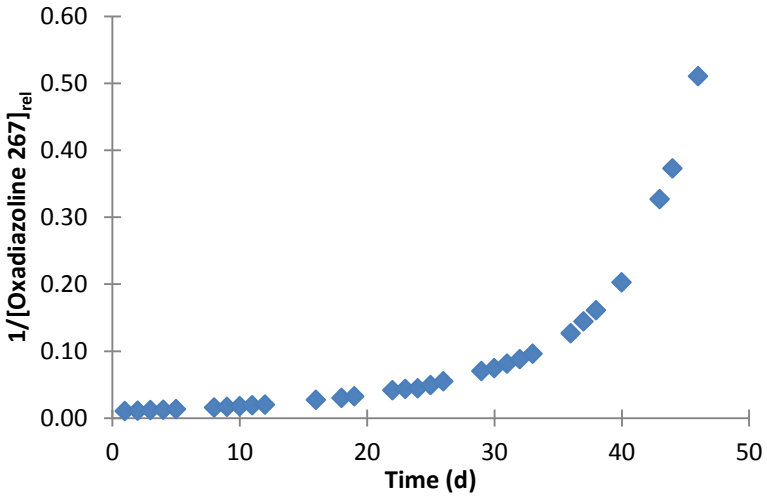


Figure 76: Second order rate check: 1/[oxadiazoline 267]$_{rel}$ *vs* time (d)

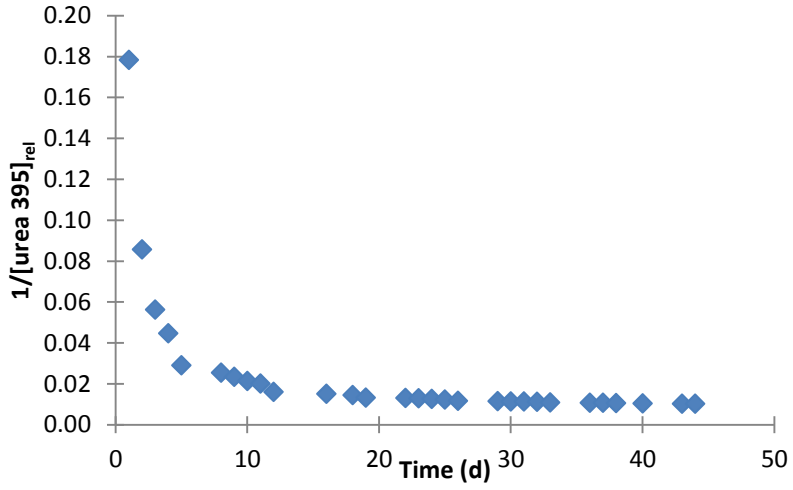
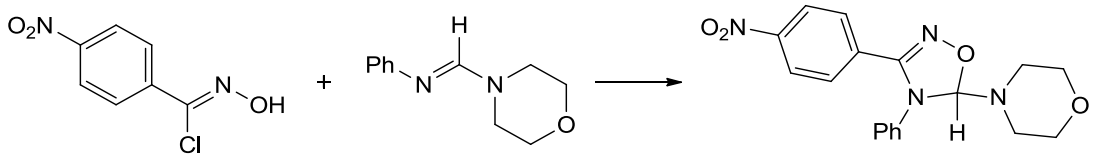


Figure 77: Second order rate check: 1/[urea 395]$_{rel}$ *vs* time (d)

To try to improve the yield of oxadiazoline **267**, the stir time of the reaction was extended (entry 2, Table 30), which gave a mixture of products. It appears as though another substance containing a morpholine group in its molecular structure is present in a 1:1 ratio with oxadiazoline **267**. The aromatic peaks were also too numerous to correlate to just the oxadiazoline alone. However, comparison with the urea **395**, amidine **341** and *N*-formylmorpholine showed that none of these were present.

The results of the reaction of *p*-nitrobenzohydroximoyl chloride **275** and amidine **341** in the preparation of oxadiazoline **392** are summarised by entries 3-5 in Table 30 (Scheme 213).

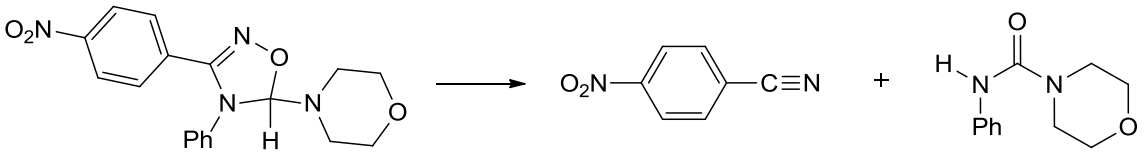


275 **341** **392**

Scheme 213: The preparation of oxadiazoline 392

With a stir time of 1.25 h, an aqueous work-up and recrystallization from ethyl acetate - hexane, the oxadiazoline was obtained as a pale yellow crystalline solid in 41% yield (Entry 3). Its spectroscopic properties were in excellent agreement with the proposed structure. The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.19 ppm as a 1H singlet in ^{1}H NMR spectrum. Reducing the stir time to ten minutes produced the oxadiazoline in just 29% yield (Entry 4). When the oxadiazoline was isolated by filtration, rather than through an aqueous work-up, a reduction in yield to 22% was seen, even

with a 1 h stir time (Entry 5). A study of the conversion of the oxadiazoline into its nitrile and urea products by time course ^{1}H NMR spectroscopic analysis was next undertaken (Scheme 214).



392 **378** **395**

Scheme 214: The decomposition of oxadiazoline 392 to nitrile 378 and urea 395

The results are shown in Figure 78. It showed that urea **395** began to form within 8 days.

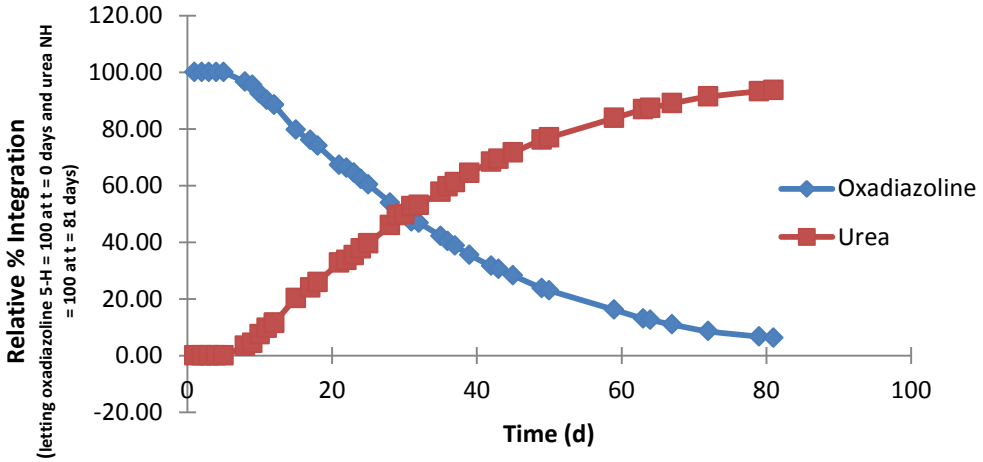


Figure 78: The conversion of oxadiazoline 392 to urea 395 at 300 K in $CDCl_3$[12]

To explore the rate of conversion of the oxadiazoline to urea, proton NMR spectroscopic analysis was the tool used. To determine the relative concentration of oxadiazoline and urea in the sample analysed, the relative integral of the heterocylic 5-H proton in oxadiazoline **392** was integrated as being equivalent to one proton in each proton NMR spectrum obtained over the time course of this study. The relative integral of the urea NH proton was then determined in comparison to the oxadiazoline 5-H proton in the same spectrum. These values were combined to give the overall total integration. The concentration of oxadiazoline, relative to that at t = 0 days, $[oxadiazoline]_{rel}$ was determined as a percentage of the oxadiazoline integration divided by the total integration, to facilitate the relative rate constant

[12] All experimental data and calculations used in the plotting of graphs in this section is outlined in Table 45.

determination. The concentration of urea, relative to that at t = 0 days, $[urea]_{rel}$ was then determined as a percentage of the urea integration divided by the total integration. For the purpose of relative rate constant determination, the molar concentration was not used, but the relative percent integration of the oxadiazoline and urea, denoted $[oxadiazoline]_{rel}$ and $[urea]_{rel}$ in the following discussion. Plotting [oxadiazoline **392**]$_{rel}$ (Figure 79) and [urea **395**]$_{rel}$ (Figure 80) *versus* time illustrates that each exhibits slightly differing behaviour. The plot of the [oxadiazoline **392**]$_{rel}$ with time portrays a much better correlation to a first order reaction, whereas the plot of [urea **395**]$_{rel}$ with time shows a biphasic property with a first-order segment later in the process.

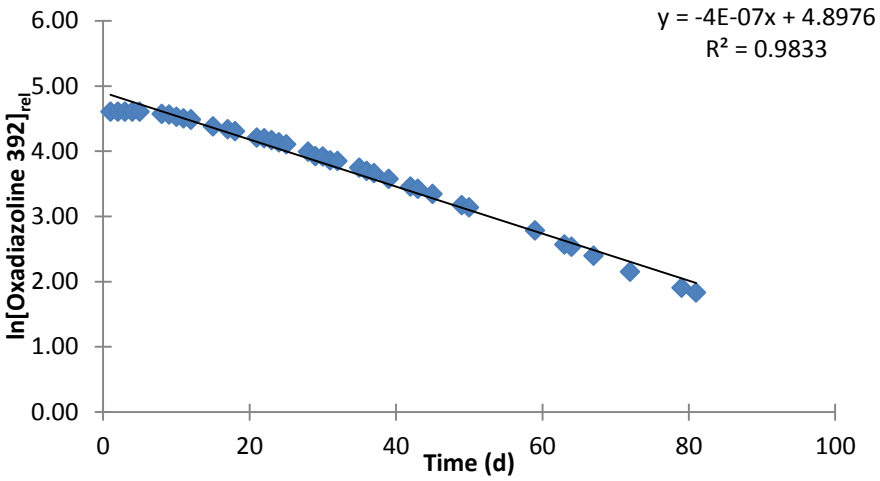


Figure 79: Determination of relative rate constant, k_{rel} by plotting ln[oxadiazoline 392]$_{rel}$ *vs* time (d) straight line fit

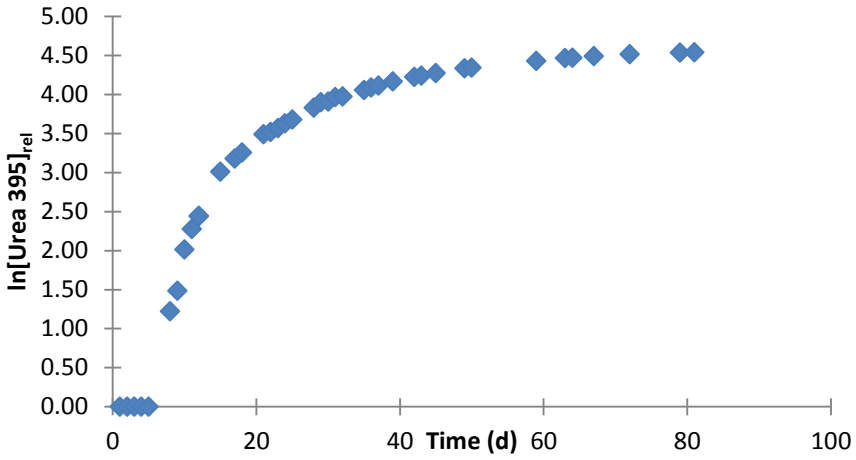


Figure 80: Determination of relative rate constant, k_{rel} by plotting ln[urea 395]$_{rel}$ *vs* time (d)

A second order plot does not give a linear correlation for either the oxadiazoline or urea (Figure 81 and Figure 82). The decomposition of oxadiazoline **392** was a first order reaction

and the relative rate constant (k_{rel} = 4 x 10^{-7} s^{-1}) was calculated from the graph of ln[Oxadiazoline **392**] *versus* time (d) (Figure 79).

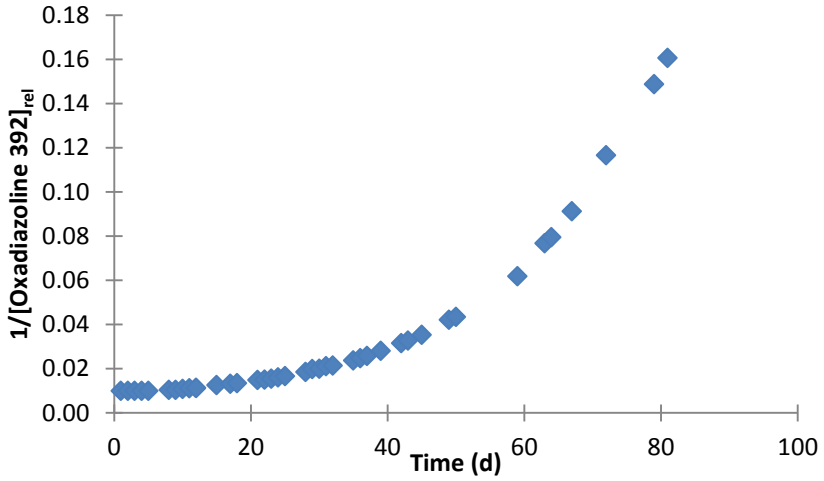


Figure 81: Second order rate check: 1/[oxadiazoline 392]$_{rel}$ *vs* time (d)

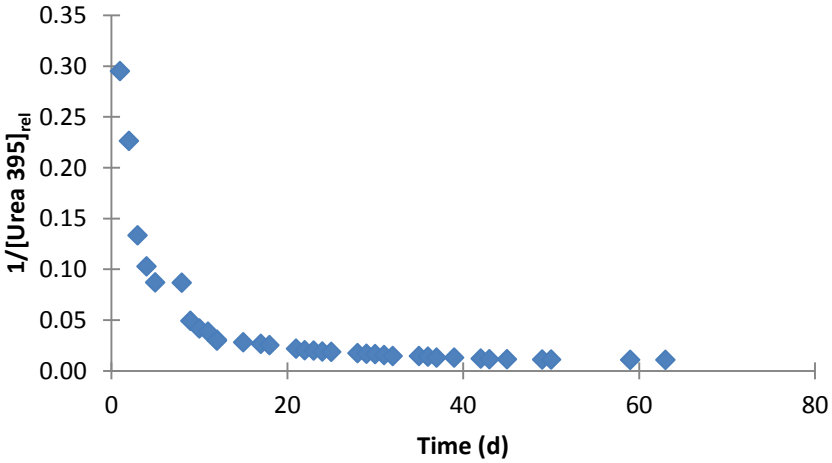
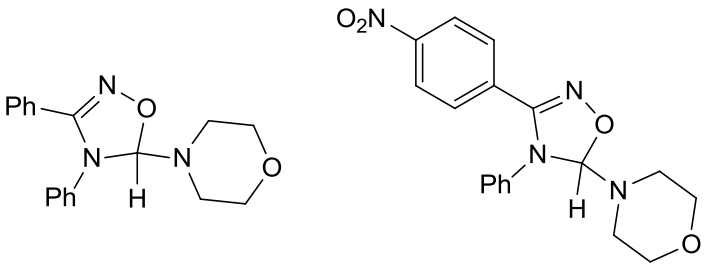


Figure 82: Second order rate check: 1/[urea 395]$_{rel}$ *vs* time (d)

The relative rate constant for oxadiazoline **392** decomposition is about half of that for oxadiazoline **267** decomposition (Figure 83).



267 **392**

Figure 83: The comparison of 267 and 392

Both oxadiazolines benefit from the stabilising effect of aromatic substituents at C_3 and N_4 of the oxadiazoline. However, oxadiazoline **392** contains a *para*-nitro substituent on the C_3 phenyl ring. The difference in electronegativity between the C_3-N and the N-O and N=O bonds of the *para*-nitro group results in electrons from the phenyl ring being pulled towards the *para*-nitro group (Figure 84). This in turn further stabilises the phenyl ring through inductive effects which accounts for the rate of decomposition of oxadiazoline **392** taking twice as long as the decomposition of oxadiazoline **267**. A second order plot does not give a linear correlation for either the oxadiazoline or urea (Figure 81 and Figure 82).

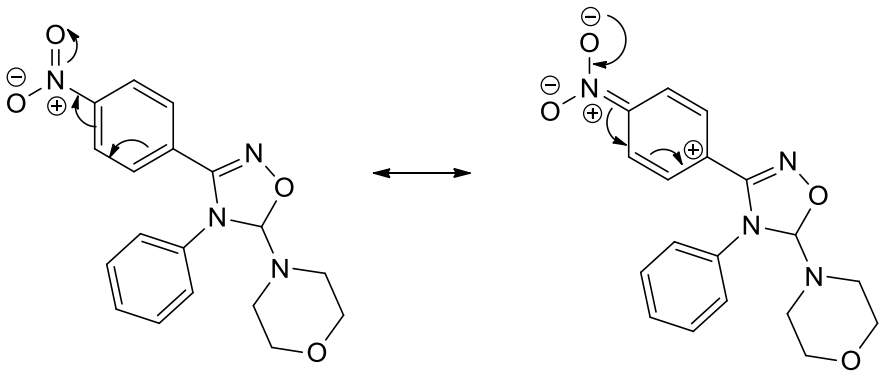
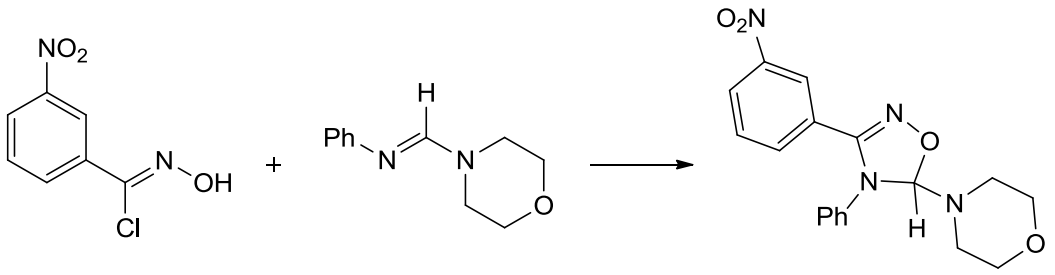


Figure 84: The stabilising effect of the *para*-nitro substituent on the C_3 phenyl in oxadiazoline 392

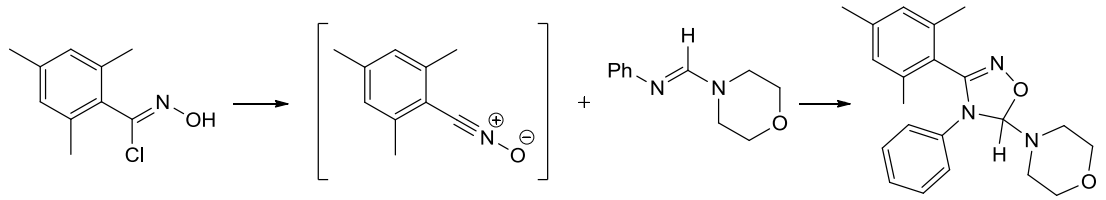
When *m*-nitrobenzohydroximoyl chloride **276** and amidine **341** were combined and stirred for 1 h (Entry 6), the oxadiazoline **393** was isolated in 59% yield as a pale yellow solid (Scheme 215). Its spectroscopic properties correlate well with its molecular structure. The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.19 ppm as a 1H singlet in ^{1}H NMR spectrum.



276 **341** **393**

Scheme 215: The synthesis of 393

Entries 7-9 illustrate the results of the reaction of 2,4,6-trimethylbenzohydroximoyl chloride **281** with amidine **341** in the attempted synthesis of oxadiazoline **393** (Scheme 216). Initially, a low temperature reaction (<10 ^{o}C) with a 1 h stir time was employed (Entry 7). Following an aqueous work-up, no characteristic oxadiazoline peak was evident in the ^{1}H NMR spectrum of the product. Comparison of the NMR spectrum with those of an authentic sample of the amidine and nitrile oxide indicated that starting materials were unchanged. This implies that mesitonitrile-*N*-oxide **7** may not react with *N*-phenylformimidoylmorpholine **341** at <10 ^{o}C. Stirring the reagents at room temperature for 1 h also returned starting materials (Entry 8). Repeating the reaction at room temperature and stirring the reaction mixture overnight yielded starting materials also (Entry 9). This suggests that the nitrile oxide **7** does not react at room temperature with amidine **341**.

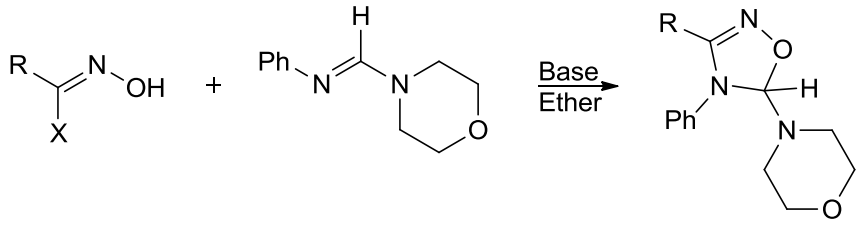


281 **7** **341** **393**

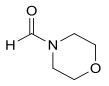
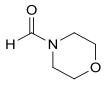
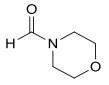
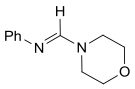
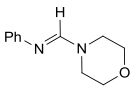
Scheme 216: The attempted synthesis of oxadiazoline 393

The results of the attempted 1,3-dipolar cycloaddition reactions of 1,3-dipoles from dihaloformaldoxime precursors, with *N*-phenylformimidoylmorpholine **341** at an addition temperature of less than 10 ^{o}C are summarised in Table 31.

Table 31: The 1,3-dipolar cycloaddition reactions of 1,3-dipoles with *N*-phenylformimidoylmorpholine 341

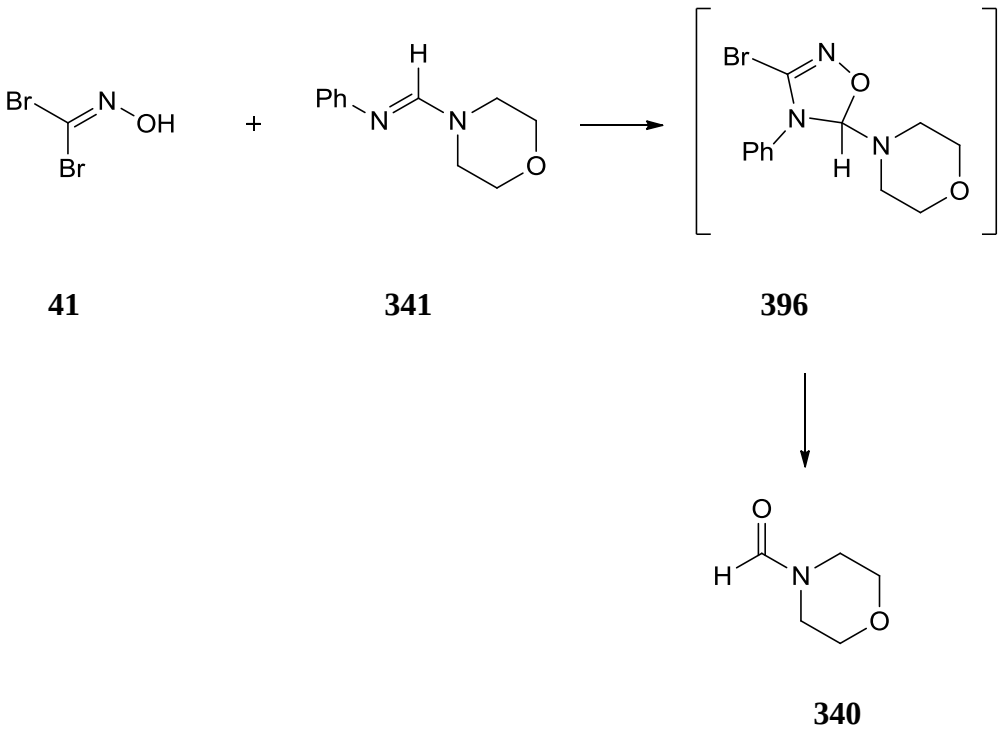


41, 16 **341** **396, 397**

Entry	Precursor	(R = X)	Base	Solvent	Stir time	Product(s)
1[13]	**41**	Br-	NEt_3	DCM	10 min	Unidentified Products
2	**41**	Br-	^tBuOK	Ether	12 h	 **340**
3	**41**	Br-	^tBuOK	Ether	1 h	 **340**
4	**41**	Br-	NEt_3	Ether	10 min	 **340**
5	**16**	Cl-	NEt_3	Ether	10 min	 **341**
6	**16**	Cl-	NEt_3	Ether	20 min	 **341**

[13] Isolated by aqueous work-up, all other entries isolated by filtration.

The reaction of dibromoformaldoxime **41** with amidine **341** was expected to produce oxadiazoline **396**, as outlined in entries 1-4 of Table 31 (Scheme 217).



41 **341** **396** **340**

Scheme 217: The attempted preparation of oxadiazoline 396

Both triethylamine and potassium *t*-butoxide were employed as bases in this reaction. The stir time of the reaction varied from ten minutes to 12 h, but the outcome was still the same. *N*-Formylmorpholine **340** was observed along with unknown product(s). Its presence was confirmed by a spiking experiment and comparison of the spectra with the spectra of the authentic sample. The electronegative effect of the bromine group at the C_3 position of oxadiazoline **396** is not sufficient to stabilise the oxadiazoline formed in the 1,3-dipolar cycloaddition reaction. The bromine atom itself contributes electron density, by means of its lone pairs of electrons, to the oxadiazoline (Figure 85). This results in too much electron density on the periphery of the five-membered ring. The net result is the breaking of the N_2-O_1 bond, in an effort to alleviate the inherent electron density of the heterocycle formed.

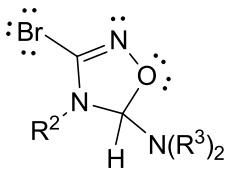
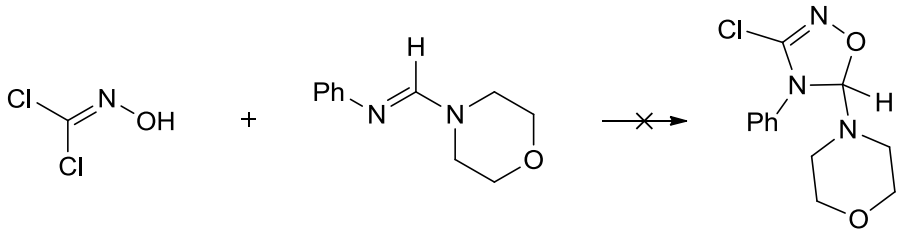


Figure 85: The distribution of the electron lone pairs in 3-bromo-oxadiazolines

Introduction of a chlorine atom at the C_3 position of the oxadiazoline (R = X = Cl) was attempted by the reaction of dichloroformaldoxime **16** with amidine **341** in the presence of triethylamine (Entries 5-6, Table 31) (Scheme 218). Both experimental procedures involved stirring the reaction mixture at room temperature and isolating the reaction product by filtration. Employing stir times of 10 min to 20 min did not yield the oxadiazoline **397**. In both cases, the amidine **341** was returned quantitatively.

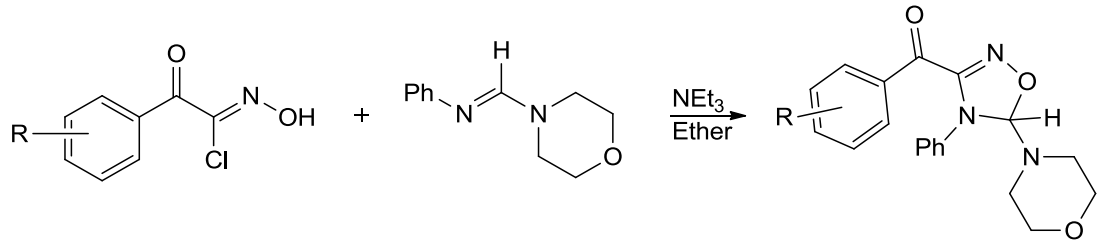


16 **341** **397**

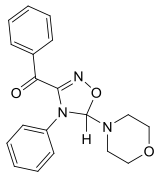
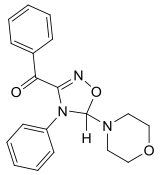
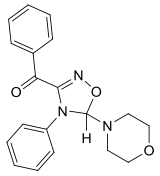
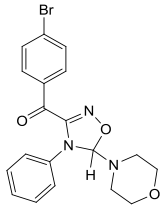
Scheme 218: The attempted preparation of oxadiazoline 397

The 1,3-dipolar cycloaddition reaction of 1,3-dipoles from 1-aroyl-1-chloroformaldoxime precursors with *N*-phenylformimidoylmorpholine **341** at an addition temperature of less than 10 ^{o}C in the synthesis of oxadiazoline **398** is portrayed in Table 32.

Table 32: The 1,3-dipolar cycloaddition reactions of 1,3-dipoles with *N*-phenylformimidoylmorpholine 341



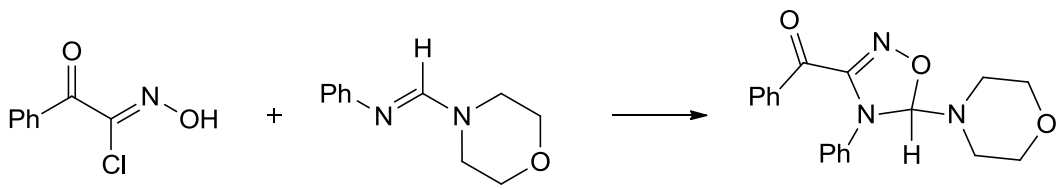
286, 292 **341** **398, 399**

Entry	Precursor	(R)	Stir time	Product(s)
1[14]	**286**	H-	1 h 40 min	 **398** 39%
2	**286**	H-	1 h	 **398** 25%
3	**286**	H-	10 min	 **398** 12%
4	**292**	*p*-Br-	10 min	 **399** 50%

Introduction of the benzoyl group at the C_3 position of the oxadiazoline was achieved by reacting 1-benzoyl-1-chloroformaldoxime **286** with amidine **341** (Entries 1-3, Table 32) in the presence of triethylamine (Scheme 219). The overall stir times range from 10 min to 1 h 40

[14] Isolated by aqueous work-up, all other entries isolated by filtration.

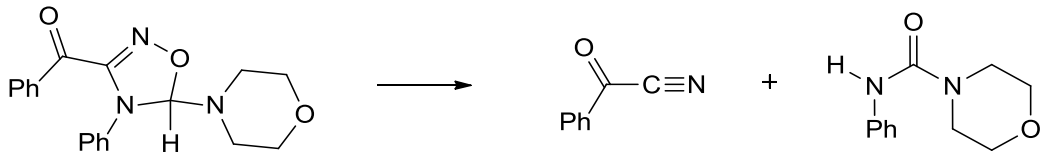
min. It was observed that the longer the stir time, the better the yield of the heterocycle (12-39%).



286 **341** **398**

Scheme 219: The reaction of 1-benzoyl-1-chloroformaldoxime 286 with amidine 341

Stirring the reagents for 1 h 40 min gave the oxadiazoline **398** in 39% yield, which was isolated as a pale yellow solid. Its melting point (94-95.5 ^{o}C) shows that it was relatively pure following recrystallization from ethyl acetate - hexane. The spectroscopic properties of the oxadiazoline are in agreement with its molecular structure. The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.26 ppm as a 1H singlet in ^{1}H NMR spectrum. HRMS identified the parent molecular ion mass at 338.1499 amu under ESI conditions. A time-course study of the formation of urea **395** from oxadiazoline **398** was next undertaken (Scheme 220).



398 **387** **395**

Scheme 220: The cycloreversion of oxadiazoline 398 to nitrile 387 and urea 395

The results are summarised in Figure 86.

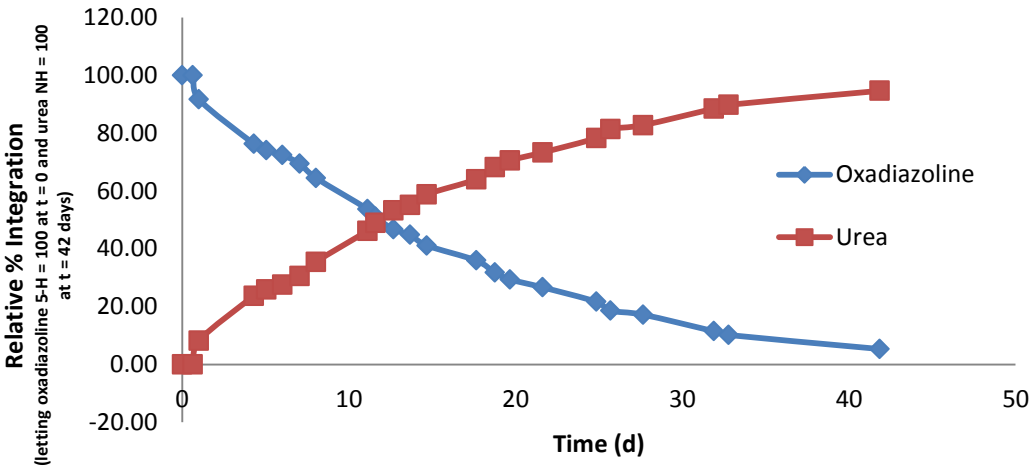


Figure 86: The conversion of oxadiazoline 398 to urea 395 at 300K in $CDCl_3$[15]

To explore the rate of conversion of the oxadiazoline to urea, proton NMR spectroscopic analysis was again used. To determine the relative concentration of oxadiazoline and urea in the sample analysed, the relative integral of the heterocylic 5-H proton in oxadiazoline **398** was integrated as being equivalent to one proton in each proton NMR spectrum obtained over the time course of this study. The relative integral of the urea NH proton was then determined in comparison to the oxadiazoline 5-H proton in the same spectrum. These values were combined to give the overall total integration. The concentration of oxadiazoline, relative to that at t = 0 days, $[\text{oxadiazoline}]_{rel}$ was determined as a percentage of the oxadiazoline integration divided by the total integration to facilitate the relative rate constant determination. The concentration of the urea, relative to that at t = 0 days, $[\text{urea}]_{rel}$ was then determined as a percentage of the urea integration divided by the total integration. For the purpose of relative rate constant determination, the molar concentration was not used, but the relative percent integration of the oxadiazoline and urea, denoted $[\text{oxadiazoline}]_{rel}$ and $[\text{urea}]_{rel}$ in the following discussion.

Plotting [oxadiazoline **398**]$_{rel}$ (Figure 87) and [urea **395**]$_{rel}$ (Figure 88) *versus* time illustrates that each exhibits slightly differing behaviour. The plot of [oxadiazoline **398**]$_{rel}$ with time portrays a much better correlation to a first order reaction, whereas the plot of [urea **395**]$_{rel}$ with time shows a biphasic property with a first-order segment later in the process.

[15] All experimental data and calculations used in the plotting of graphs in this section is outlined in Table 46.

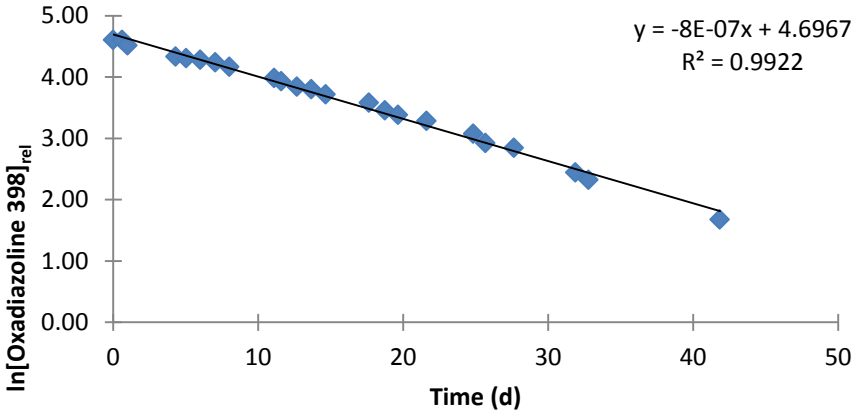


Figure 87: The determination of first order relative rate constant of the conversion of oxadiazoline 398 to urea 395, by plotting ln [oxadiazoline 398]$_{rel}$ *vs* time (d) with a straight line fit

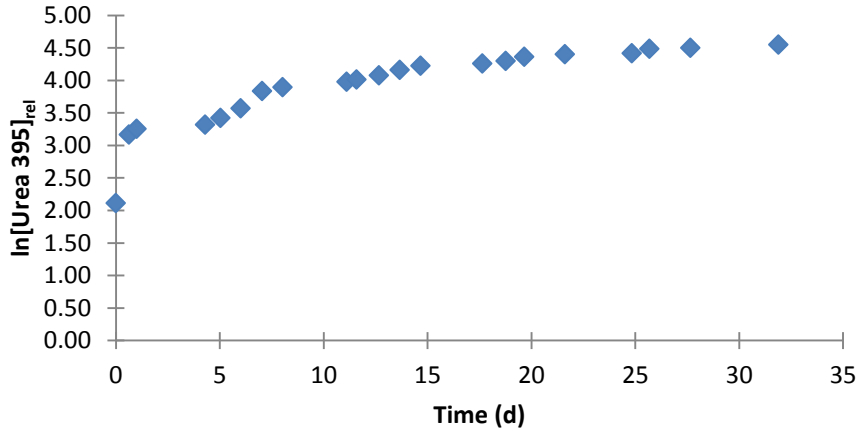


Figure 88: The determination of first order relative rate constant of the conversion of oxadiazoline 398 to urea 395, by plotting ln [urea]$_{rel}$ *vs* time (d)

A second order plot does not give a linear correlation for either the oxadiazoline or urea (Figure 89 and Figure 90). The decomposition of oxadiazoline **398** is a first order reaction and a relative rate constant (k_{rel} = 8 x 10^{-7} s^{-1}) was calculated from the graph of ln[oxadiazoline **398**]$_{rel}$ *versus* time (d) (Figure 87).

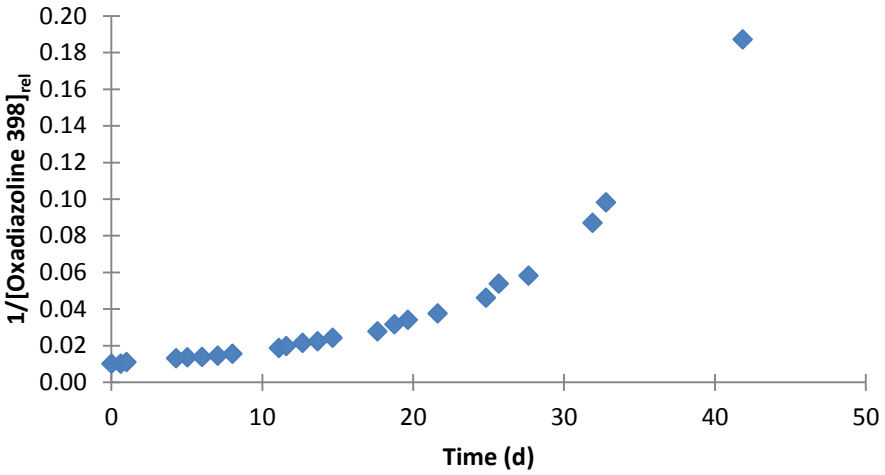


Figure 89: Second order rate check of the conversion of oxadiazoline 398 to urea 395, by plotting 1/[oxadiazoline 398]$_{rel}$ *vs* time (d)

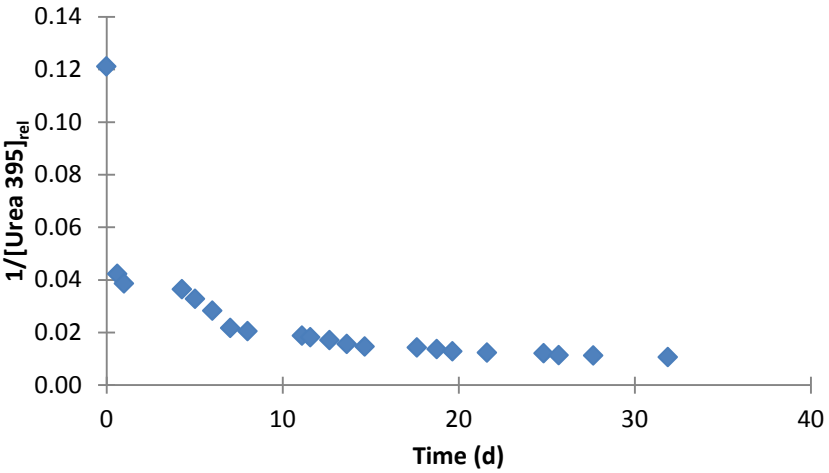
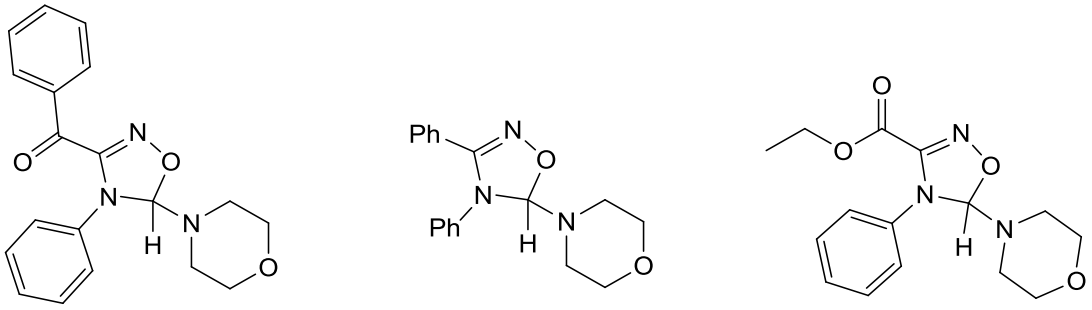


Figure 90: Second order rate check of the conversion of oxadiazoline 398 to urea 395, by plotting 1/[urea 395]$_{rel}$ *vs* time (d)

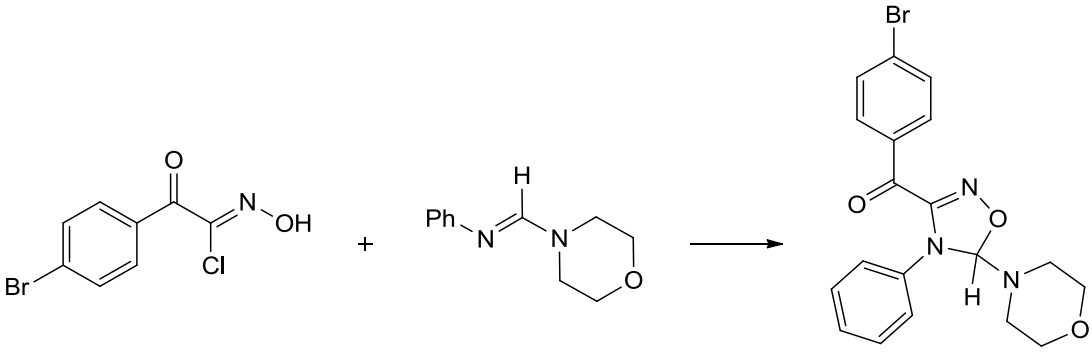
The relative rate constant for the 3-benzoyl compound **398** is about the same as that for the corresponding 3-phenyl compound **267** even though the former substituent is more electron withdrawing (Figure 91). Interestingly, the 3-ethoxycarbonyl analogue **400** which has a similar substitution pattern to **398** is less reactive: k_{rel}(**398** decomposition/**400** decomposition) ≈ 30.



398 **267** **400**

Figure 91: The comparison of 398, 267 and 400

1-(*p*-Bromobenzoyl)-1-chlorofomaldoxime **292** as a nitrile oxide precursor was included in the study (Scheme 221). It was anticipated that including an electron-withdrawing substituent in the *para* position of the phenyl group would increase the stability of the corresponding nitrile oxide, such that its rate of cycloaddition with amidine **341** in the attempted preparation of oxadiazoline **399** could be studied by NMR spectroscopy.

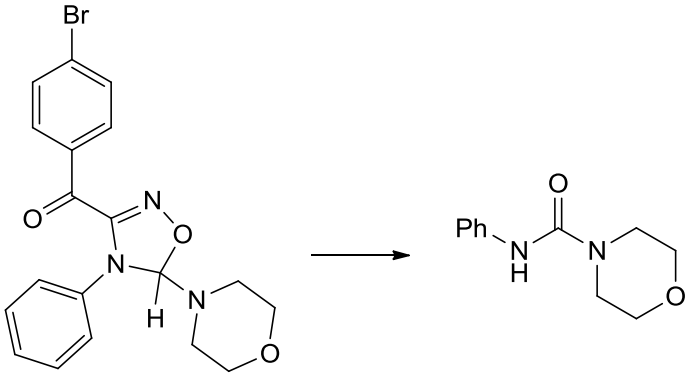


292 **341** **399**

Scheme 221: The preparation of oxadiazoline 399

NMR spectroscopy studies (Entry 4, Table 32) suggest heterocycle formation within 10 minutes, subsequent isolation gave oxadiazoline **399** as a pale orange solid in 50% yield. Its melting point 90-92^{o}C confirming that recrystallization from chloroform - hexane gave the oxadiazoline in good purity. Its spectroscopic properties were in excellent agreement with the molecular structure. The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.58 ppm as a 1H singlet in ^{1}H NMR spectrum. The mass spectrum of **399**, under ESI conditions showed a typical ion pattern characteristic of a compound containing one bromine atom in its molecular structure. Attempted HRMS analysis

of the molecular ion species produced evidence for the urea **395**, i.e. the compound decomposed under the MS analysis conditions.

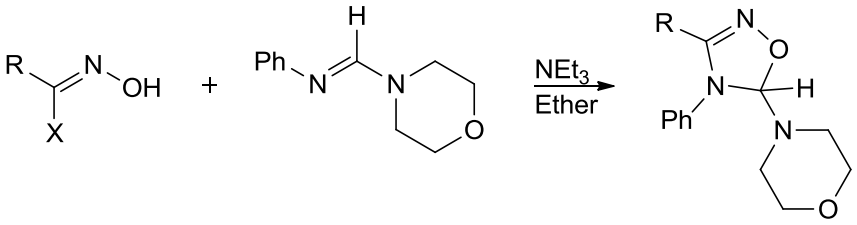


399 **395**

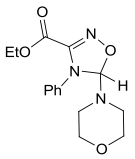
Scheme 222: The decomposition of 399 to 395

The 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from other hydroximoyl halide precursors, with *N*-phenylformimidoylmorpholine **341** at an addition temperature of <10 °C is outlined in Table 33.

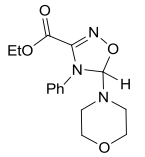
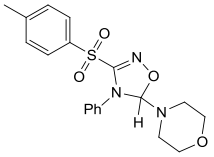
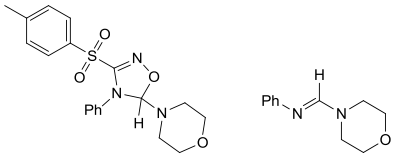
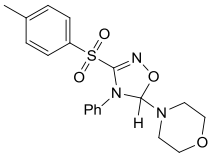
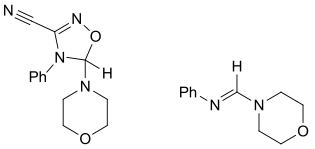
Table 33: The results of the reaction of other hydroximoyl halides with *N*-phenylformimidoylmorpholine 341



295, 299, 304 **341** **400, 401, 402**

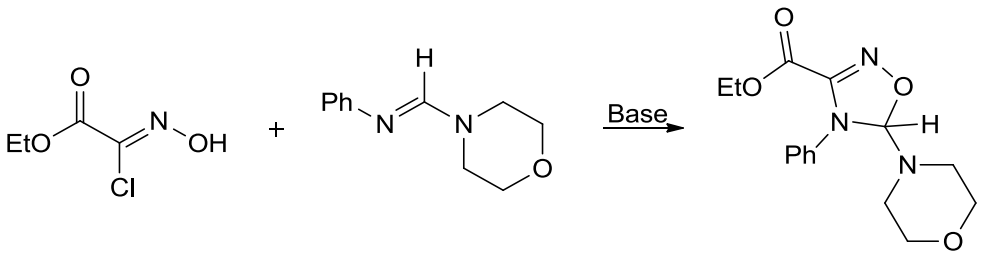
Entry	Precursor	(R)	X	Stir time	Isolation method[16]	Product(s)
1	**295**	EtO_2C-	Cl-	10 min	A	 **400** 10%

[16] Method A indicates an aqueous work up, method B indicates isolation by filtration.

Entry	Precursor	(R)	X	Stir time	Isolation method[17]	Product(s)
2	**295**	EtO_2C-	Cl-	1 h	B	 **400** 56%
3	**299**	Ts-	Br-	5 min	A	 **401** 83%
4	**299**	Ts-	Br-	1 h	B	 **401** **341** (36 : 64)
5	**299**	Ts-	Br-	32 min	B	 **401** 42%
6	**304**	NC-	Cl-	10 min	B	 **402** **341** (48 : 52)

Ethylchloroglyoxalate oxime **295** and *N*-phenylformimidoylmorpholine **341** were combined (Entries 1-2, Table 33) in an effort to prepare oxadiazoline **400** (Scheme 223). Stirring the reagents together for ten minutes at room temperature followed by an aqueous work-up and recrystallisation from ethyl acetate and hexane yielded the oxadiazoline (Entry 1) (m.p. 105-105.5°C) in 10% yield as a white crystalline solid. Increasing the stir time at room temperature to 1 h (Entry 2) also increased the yield to 56%.

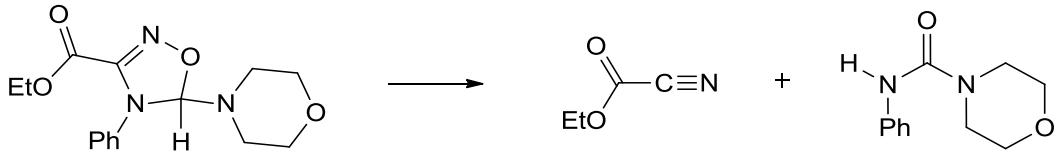
[17] Method A indicates an aqueous work up, method B indicates isolation by filtration.



295 **341** **400**

Scheme 223: The reaction of oxime 295 with amidine 341

The spectroscopic properties of oxadiazoline **400** were in excellent agreement with the molecular structure and the HRMS analysis produced an ion of mass 306.1464 amu (M+1) under ESI conditions. The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.17 ppm as a 1H singlet in its ^{1}H NMR spectrum. A ^{1}H NMR spectroscopy study of the conversion of oxadiazoline **400** (Scheme 224) showed that it took ten days at room temperature before a steady rate of decomposition to the urea **395** was achieved.



400 **403** **395**

Scheme 224: The conversion of oxadiazoline 400 to nitrile 403 and urea 395

The results are summarised in Figure 92.

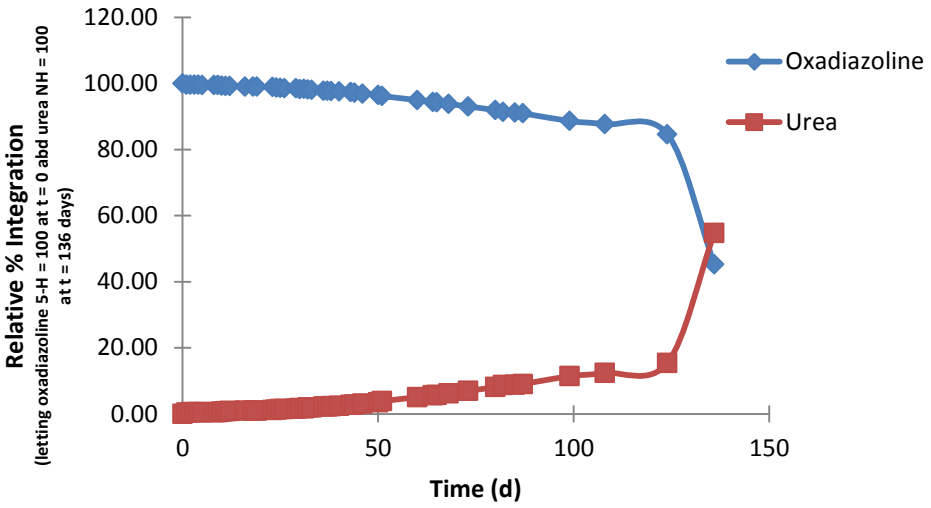


Figure 92: The conversion of oxadiazoline 400 to urea 395 in $CDCl_3$ at 300K over time (d)[18]

To determine the relative concentration of oxadiazoline and urea in the sample analysed, the relative integral of the heterocylic 5-H proton in oxadiazoline **400** was integrated as being equivalent to one proton in each proton NMR spectrum obtained over the time course of this study. The relative integral of the urea NH proton was then determined in comparison to the oxadiazoline 5-H proton in the same spectrum. These values were combined to give the overall total integration. The concentration of oxadiazoline, relative to that at t =0 days, $[\text{oxadiazoline}]_{rel}$ was determined as a percentage of the oxadiazoline integration divided by the total integration to facilitate the relative rate constant determination. The concentration of urea, relative to that at t =0 days, $[\text{urea}]_{rel}$ was then determined as a percentage of the urea integration divided by the total integration. For the purpose of relative rate constant determination, the molar concentration was not used, but the relative percent integration of the oxadiazoline and urea, denoted [oxadiazoline **400**]$_{rel}$ and [urea **395**]$_{rel}$ in the following discussion.

The plot of ln[oxadiazoline **400**]$_{rel}$ *versus* time portrays a good correlation to a first order reaction, however, the R^2 value indicates that the straight line fit is poor (Figure 93). The plot of ln[urea **395**]$_{rel}$ *versus* time shows a better correlation to a first-order reaction (Figure 94).

[18] All experimental data and calculations used in the plotting of graphs in this section is outlined in

Table 47.

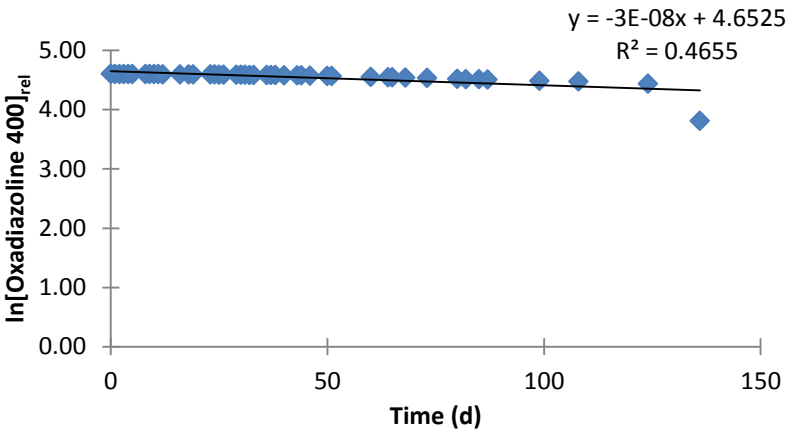


Figure 93: The determination of relative rate constant of the conversion of oxadiazoline 400 to urea 395 by plotting ln[oxadiazoline 400]$_{rel}$ *vs* time (d) with a straight line fit

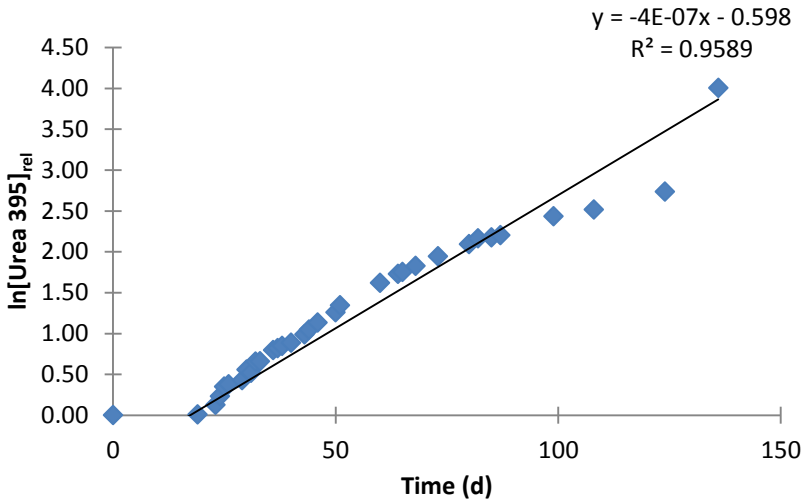


Figure 94: The determination of relative rate constant of the conversion of oxadiazoline 400 to urea 395 by plotting ln[urea 395]$_{rel}$ *vs* time (d) with a straight line fit

A second order plot does not give a linear correlation for either the oxadiazoline or urea (Figure 95 and Figure 96). The decomposition of oxadiazoline **400** is a first order reaction and a relative rate constant (k_{rel} = 4 x 10^{-7} s^{-1}) was determined from the graph of ln[urea **395**]$_{rel}$ *versus* time (d) (Figure 94).

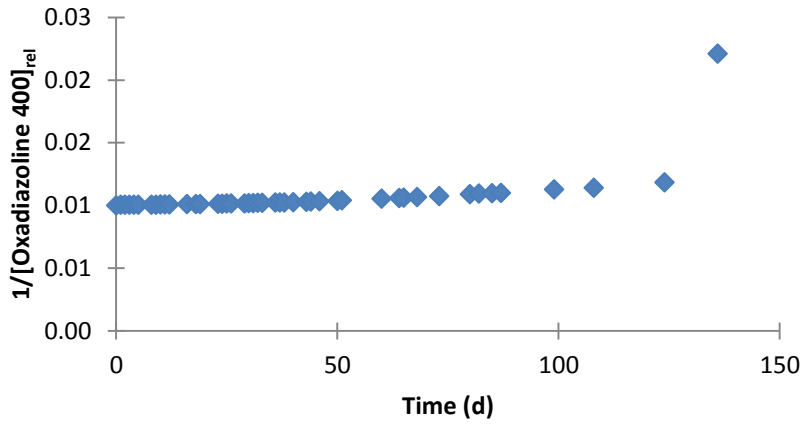


Figure 95: Second order relative rate constant check of the conversion of oxadiazoline 400 to urea 395: 1/[oxadiazoline 400]$_{rel}$ *vs* time (d)

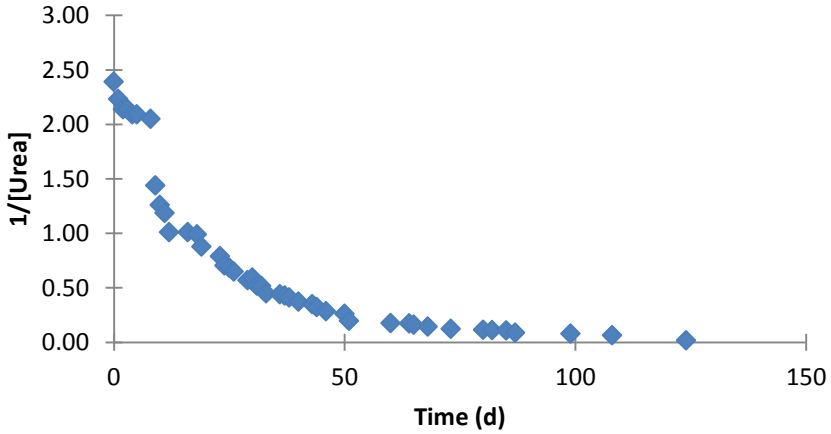
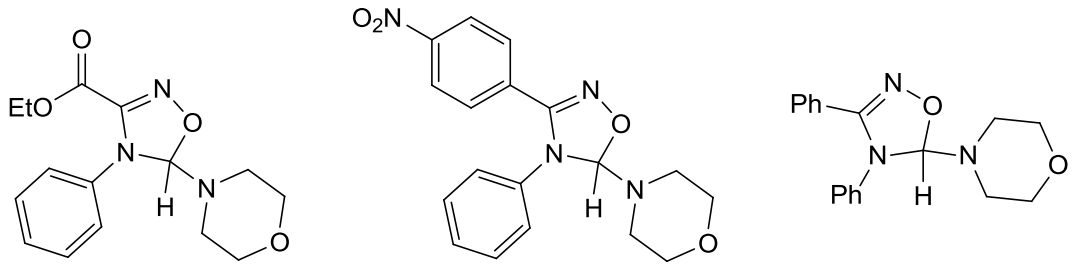


Figure 96: Second order relative rate constant checkof the conversion of oxadiazoline 400 to urea 395 by plotting 1/[urea 395]$_{rel}$ *vs* time (d)

The relative rate constant for **400** decomposition is one tenth of that for the 3-nitrophenyl oxadiazoline **392** and thirty times less than that for the 3-phenyl compound **267** (Figure 97).



400 **392** **267**

Figure 97: The structures of 400, 392 and 267

Resonance delocalisation of the lone pair of electrons on the oxygen of the ester moiety provides sufficient stabilisation for oxadiazoline **400** (Figure 98). This factor, coupled to the moderate electron-withdrawing effect of the ester group account for oxadiazoline **400** having a decomposition rate that is ten times slower than the 3-nitrophenyl-oxadiazoline **392** and thirty times slower that the 3-phenyl oxadiazoline **267**.

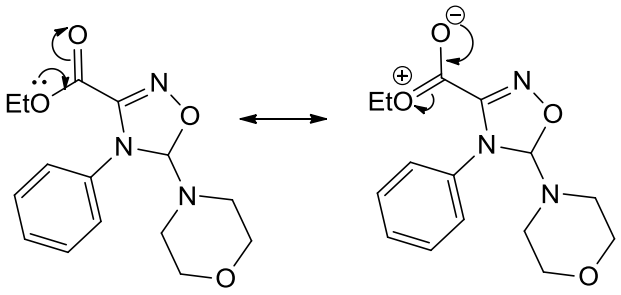
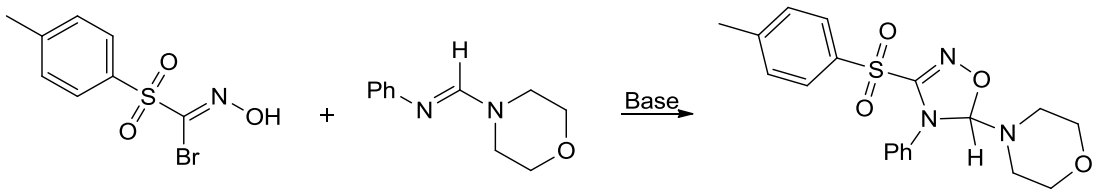


Figure 98: The resonance delocalisation of the ester group which contributes to the increased stability of oxadiazoline 400

Entries 3-5 in Table 33 chart the results of the reaction of 1-*p*-toluenesulfonyl-1-bromoformaldoxime **299** with amidine **341** in the preparation of oxadiazoline **401** (Scheme 225). Reaction stir times varied from ten minutes to one hour. The optimum reaction was found to involve a stir time of 32 min, isolation by filtration (Entry 5) and recrystallization from ethyl acetate - hexane. This gave the oxadiazoline **401** in 42% yield as a pale yellow solid. Its melting point was 70-72 ^{o}C. The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.15 ppm as a 1H singlet in its ^{1}H NMR spectrum. The parent molecular ion was observed at 388 amu under nominal mass spectral conditions. The spectroscopic properties of the compound were consistent with its molecular structure.

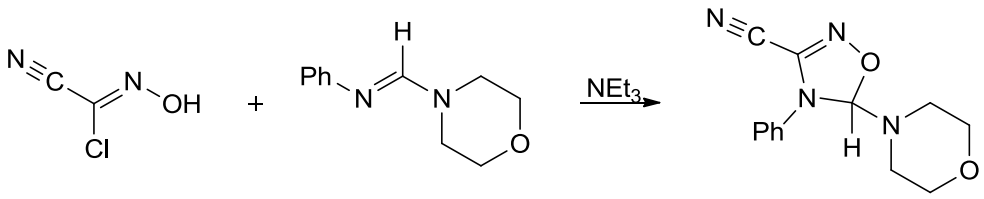


299 **341** **401**

Scheme 225: The reaction of 299 with amidine 341

The attempted preparation of oxadiazoline **402** is outlined in entry 6 of Table 33. This involved the reaction of cyanoformohydroximoyl chloride **304** with amidine **341** in the presence of triethylamine (Scheme 226). Following recrystallization from ether - hexane, a mixture of the oxadiazoline **402** and amidine **341** was isolated as a yellow solid in a ratio of

48 : 52. The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.38 ppm as a 1H singlet in its ^{1}H NMR spectrum. The spectroscopic properties for the oxadiazoline are in agreement with the molecular structure. The oxadiazoline structure was also confirmed by HRMS analysis (M+1) = 259.1189 amu under ESI conditions.

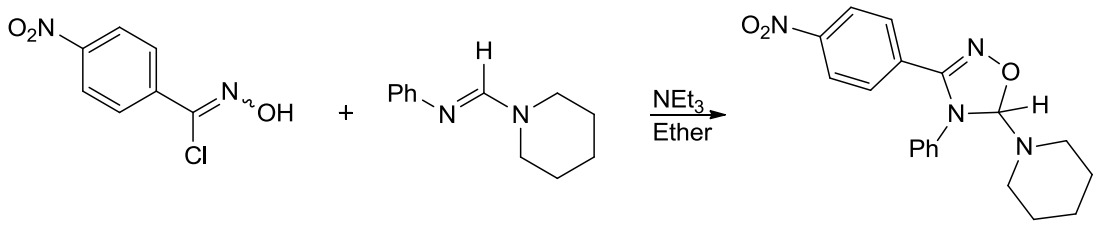


304 **341** **402**

Scheme 226: The attempted preparation of oxadiazoline 402

4.1.4 Reactions of *N*-phenylformimidoylpiperidine with *p*-nitrobenzohydroximoyl chloride

To investigate the effect of a slightly less electron withdrawing group at the C-5 position of the oxadiazoline, a piperidine ring was used in the place of the previously investigated morpholine ring. The introduction of a piperidine ring at the C-5 position of the oxadiazoline was explored by using *N*-phenylformimidoylpiperidine **343** as the dipolarophile in the formation of oxadiazoline **404** (Scheme 227). Oxadiazoline **404** was formed by the reaction of *p*-nitrobenzohydroximoyl chloride **275** and *N*-phenylformimidoylpiperidine **343** in the presence of base.

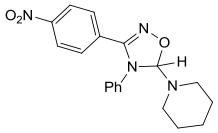
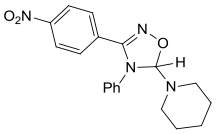
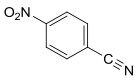
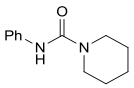


275 **343** **404**

Scheme 227: The reaction of 275 and *N*-phenylformimidoylpiperidine 343

The results of this cycloaddition reaction at an addition temperature of <10 °C and isolation by filtration are outlined in Table 34.

Table 34: The effect of different reaction stir times on the reaction outcome

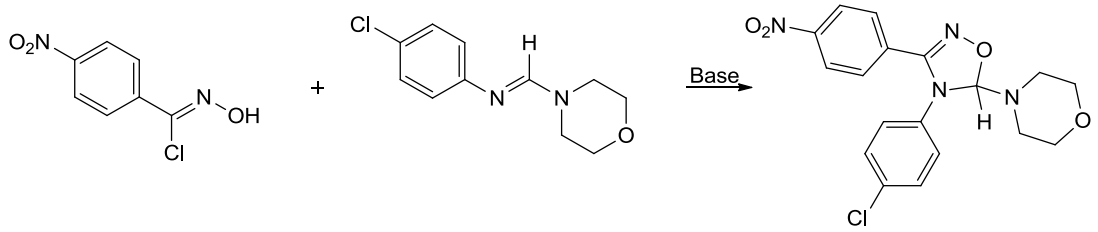
Entry	Stir time	Product (s)
1	10 min	 **404** 62%
2	1 h	 **404**  **378**  **337** (38 : 31 : 31)

Stirring the reaction mixture for ten minutes gave the oxadiazoline **404** in 62% yield. However, drying the solid under high vacuum after recrystallization gave a mixture of results suggesting that conversion of the oxadiazoline into the nitrile **378** and the urea **337** occurred during the recrystallisation and drying operations. This mixture of products were purified by column chromatography and the nitrile **378** and the urea **337** were isolated. Increasing the stir time of the 1,3-dipolar cycloaddition reaction to 1 h, yielded the oxadiazoline **404**, nitrile **378** and urea **337** in a ratio of (38 : 31 : 31). The spectroscopic properties pertaining to the oxadiazoline **404** were in excellent correlation with the molecular structure. The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.20 ppm as a 1H singlet in ^{1}H NMR spectrum. In comparison to the morpholine derivative, the piperidine derived oxadiazoline partly decomposed on handling, consistent with earlier observations that electron donating groups at C-5 in the heterocyclic ring accelerate the rate of conversion of the oxadiazoline into the nitrile and urea products.

4.1.5 Reactions of *N*-*p*-chlorophenylformimidoylmorpholine with *p*-nitrobenzohydroximoyl chloride

In an attempt to positively influence the stability of the oxadiazoline generated by the 1,3-dipolar cycloaddition of nitrile oxides with formamidines, the type of formamidine explored in this study was expanded to include *N*-*p*-chlorophenylformimidoylmorpholine **345** (Scheme 228). The addition of an electron-withdrawing *para*-chlorine group on the phenyl at the N_4 position of the oxadiazoline ring was anticipated to further stabilise the oxadiazoline formed. This study was explored by the reaction of *p*-nitrobenzohydroximoyl chloride **275** with amidine **345** to afford oxadiazoline **405**. NMR spectroscopy studies suggest heterocycle

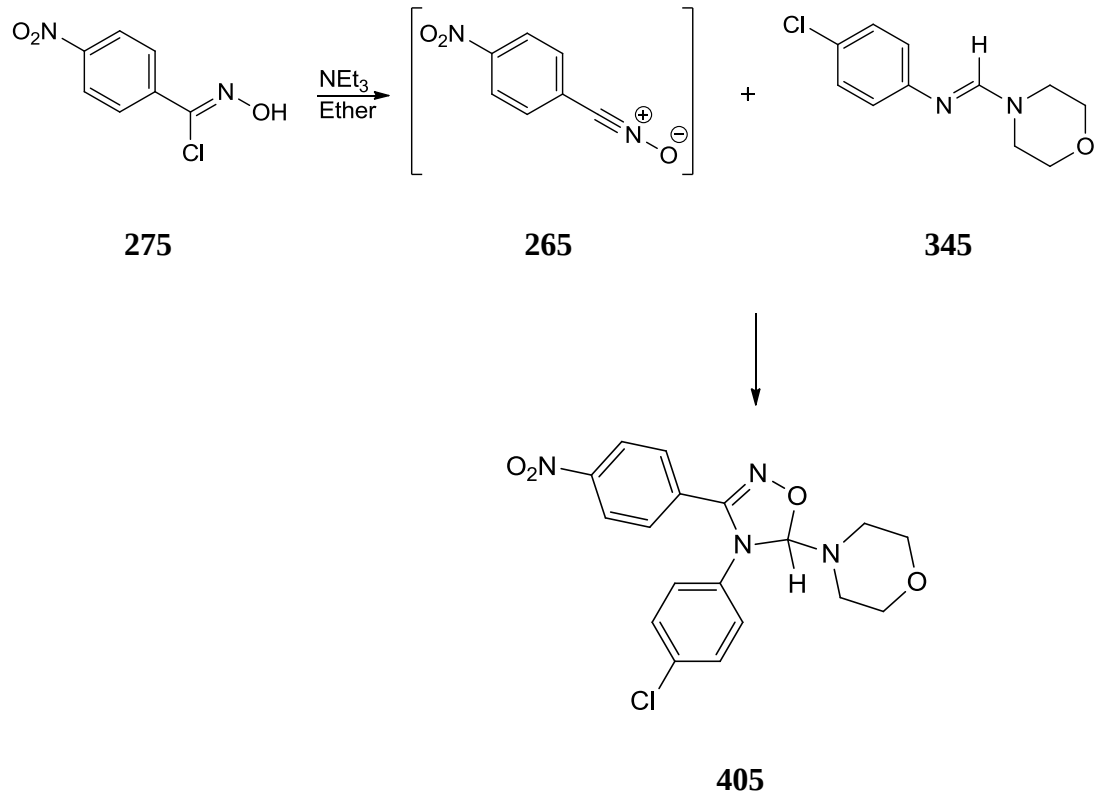
formation within 10 minutes, subsequent isolation gave oxadiazoline **405** as a pale yellow crystalline solid in 3% yield. Stirring the reaction mixture for up to 2 h 10 min (Entry 2) resulted in a marginal increase in the isolated yield of the product (3% to 4%). A poor recrystallisation is the primary cause of this low yield as the ^{1}H NMR spectroscopic data indicated that the oxadiazoline **405** was the only product of this reaction as all starting materials had been consumed.



275 **345** **405**

Scheme 228: The reaction of 275 and *N*-*p*-chlorophenylformimidoylmorpholine 345

The oxadiazoline **405** was isolated as a pale yellow crystalline solid. Its melting point (123-147 ^{o}C) was broad. The characteristic oxadiazoline proton attached to the C-5 in the oxadiazoline was observed at 6.15 ppm as a 1H singlet in ^{1}H NMR spectrum. The NMR spectra were assigned with the aid of HSQC and HMBC analysis and the spectroscopic properties were in agreement with the structure. The exact mass was calculated for $C_{18}H_{17}N_4O_4{}^{35}Cl$ $[M+H]^+$ 389.1017 a.m.u. and a value of 389.1003 a.m.u was found under ESI conditions. The aim was to introduce a moderately electron-withdrawing substituent in the amidine so that the rate of reaction with the nitrile oxide with regards to the parent *N*-phenyl-morpholino amidine (**341**) could be sufficiently slowed as to allow the reaction to be studied by ^{1}H NMR spectroscopy. An NMR spectroscopy tube reaction (outlined in detail further on in this chapter – see page 213) showed that after addition of the nitrile oxide **265** solution to the amidine, the oxadiazoline **405**, amidine **345** and nitrile oxide **265** were present, 9 min after the beginning of the reaction (Scheme 229). This supports the reasoning employed in including this amidine in the study, i.e. that electron withdrawing substituents on the imino nitrogen of the amidine reduces the rate of the cycloaddition.



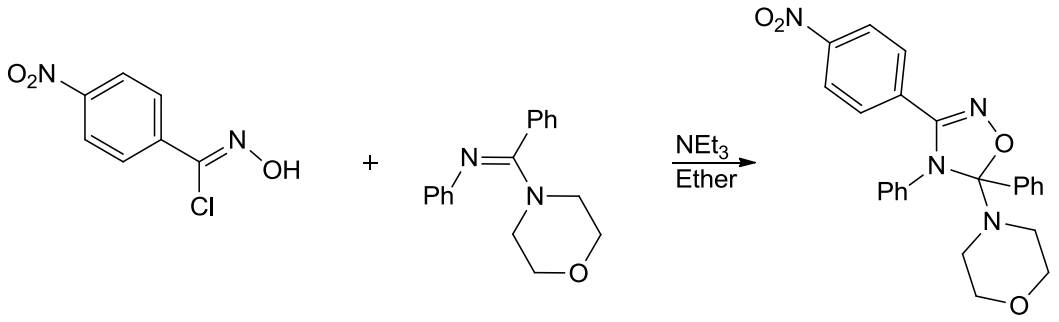
Scheme 229: The reaction of 275 and *N*-*p*-chlorophenylformimidoylmorpholine 345

4.2 1,3-Dipolar cycloaddition reactions with benzamidines

The introduction of a phenyl group in place of the hydrogen at the C-5 position of the oxadiazoline ring was explored in an effort to observe if it would introduce a positive stabilisation effect.

4.2.1 Reactions with *N*-(*N´*-phenylbenzimidoyl)-morpholine

The result of the reaction of a substituted benzohydroximoyl halide **275** with *N*-(*N´*-phenylbenzimidoyl)-morpholine **349** at an addition temperature of <10°C is summarised in Scheme 230. The oxadiazoline was isolated as a yellow crystalline solid after recrystallization from chloroform - hexane in 7% yield, its melting point 180-181 ^{o}C. The spectroscopic properties are in excellent agreement with the literature data for the compound. The exact mass was calculated for $C_{24}H_{22}N_4O_4$ $[M+H]^+$ 431.1719 a.m.u. and a value of 431.1722 a.m.u was found under ESI conditions.

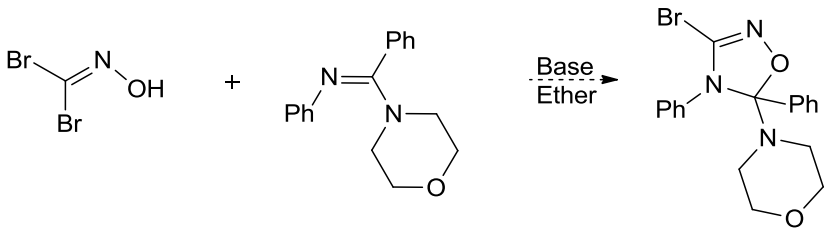


275 **349** **406**

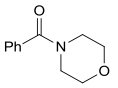
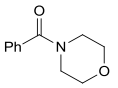
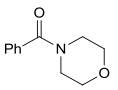
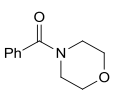
Scheme 230: The reaction of *p*-nitrobenzohydroximoyl chloride 275 with benzamidine 349

The results of the reaction of a dihaloformaldoxime with *N*-(*N´*-phenylbenzimidoyl)-morpholine **349** at an addition temperature of <10°C are summarised in Table 35.

Table 35: The reaction of dibromoformaldoxime 41 with *N*-(*N´*-phenylbenzimidoyl)-morpholine 349 in the presence of different bases

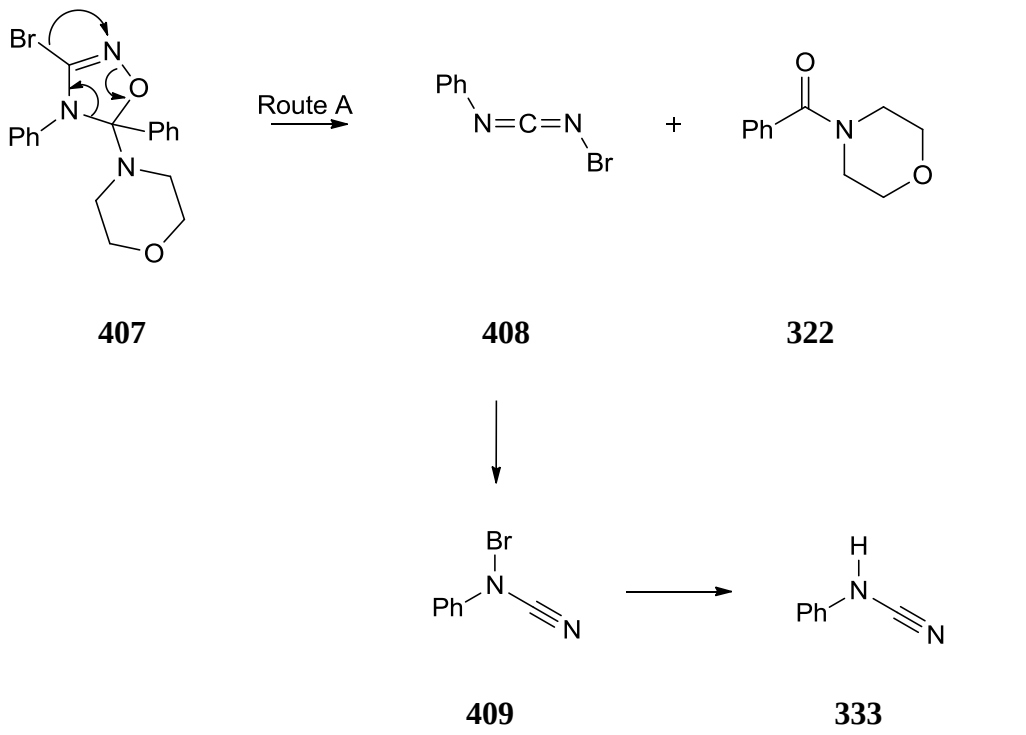


41 **349** **407**

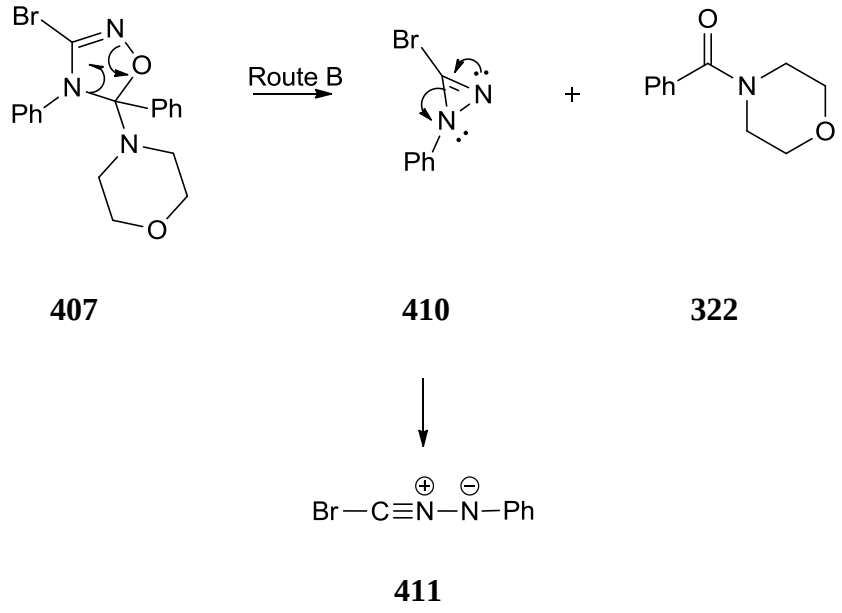
Entry	Base	Stir time	Product(s)
1	NEt_3	10 min	 **322**
2	^tBuOK	10 min	 **322**
3	NEt_3	0 min[19]	 **322**
4	^tBuOK	0 min[20]	 **322**

[19] 0 min stir time refers to the reaction mixture being filtered immediately once the addition of the dihalformaldoxime solution had been completed.
[20] 0 min stir time refers to the reaction mixture being filtered immediately once the addition of the dihalformaldoxime solution had been completed.

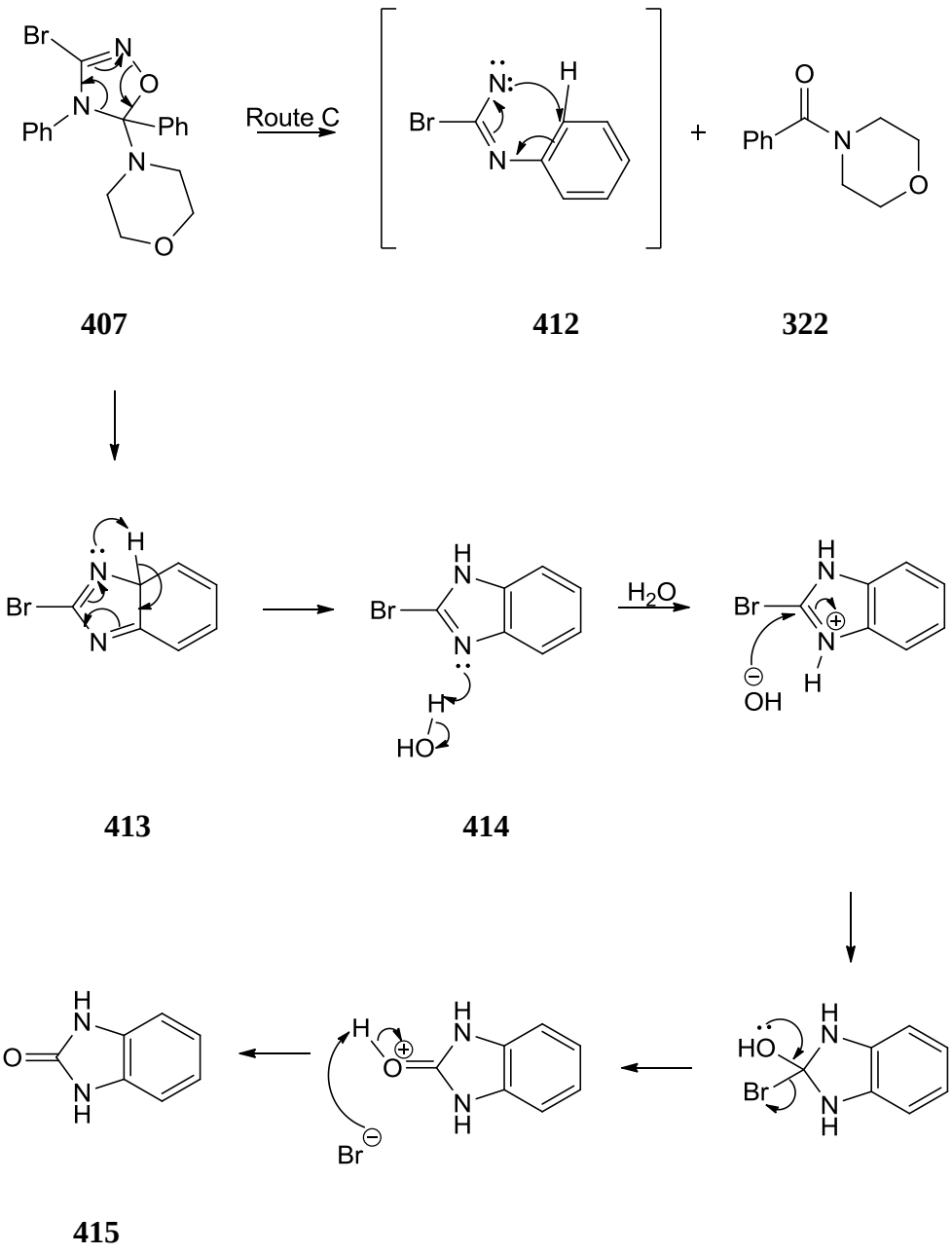
The reactions employed to incorporate a bromine substituent at the C-3 position of the oxadiazoline are outlined by entries 1-4 in Table 35. The preparation of oxadiazoline **407** was attempted by mixing dibromoformaldoxime **41** with the benzamidine **349** in the presence of a base; triethylamine and potassium *t*-butoxide were employed. The stir time of the reactions varied from 10 min to 0 min. Entry 1 illustrates the use of triethylamine as the base with a stir time of 10 min. The crude reaction product was purified by column chromatography on silica gel with ethyl acetate - hexane as eluent. Initially, 20:80 ethyl acetate:hexane was the mobile phase, which was gradually increased as elution continued to 60:40 ethyl acetate:hexane. Two separate fractions were isolated. The first was a mixture of predominantly *N*-(*N´*-phenylbenzimidoyl)-morpholine **349** and a small quantity of *N*-benzoylmorpholine **322**. The second fraction was a mixture of predominantly *N*-benzoylmorpholine **322** and a small quantity of *N*-(*N´*-phenylbenzimidoyl)-morpholine **349**. This suggests that *N*-benzoylmorpholine **322** is a product of the decomposition of the oxadiazoline. As there was not any evidence for the oxadiazoline **407**, the stir time of the reaction was reduced to aid the potential isolation of the heterocycle. Entry 3 shows the results of not stirring the reaction mixture and immediately working up the reaction after addition of the reagents. In this case, a mixture of *N*-benzoylmorpholine **322** and unknown product(s) formed. When potassium *t*-butoxide was utilised as the (Entries 2 and 4), *N*-benzoylmorpholine **322** was isolated regardless of stir time. This implies that the oxadiazoline could spontaneously undergo conversion to the amide and other products once the reagents are mixed together. The other products were not isolated nor identified but could be the *N*-bromocarbodiimide **408** (Scheme 231), a diazirine **410** or its ring opened isomer, the nitrilimine **411** (Scheme 232) – expected to be of short lifetime and likely to convert into a hydrazide through reaction with water. This is based on the understanding that bromine has a better migratory aptitude in 1,2-rearrangements. In addition, an imidazole **414** or an imidazolone **415** could arise through cyclisation of a putative imidoyl nitrene intermediate **412** to the *ortho*-position of the aromatic ring (Scheme 233).



Scheme 231: Putative route A mechanism of decomposition of oxadiazoline 407



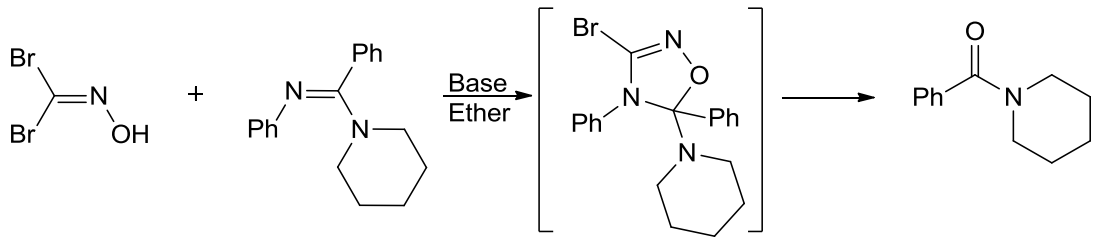
Scheme 232: Putative route B mechanism of decomposition of oxadiazoline 407



Scheme 233: Putative route C mechanism of decomposition of oxadiazoline 407

4.2.2 Reactions with *N*-(*N´*-phenylbenzimidoyl)-piperidine

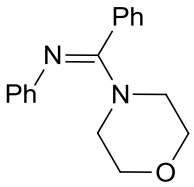
The interaction of dibromoformaldoxime **41** with *N*-(*N´*-phenylbenzimidoyl) - piperidine **350** in the attempted synthesis of oxadiazoline **416** is displayed in Scheme 234.



41 **350** **416** **324**

Scheme 234: The reaction of dibromoformaldoxime 41 with *N*-(*N´*-phenylbenzimidoyl) - piperidine 350

The results illustrate that the cycloaddition reaction appears to be followed by a rapid conversion yielding the amide **324** in line with the outcome observed from amidine **349**, regardless of which base - triethylamine or potassium *t*-butoxide - is used (Figure 99). Comparison of the ^{1}H NMR spectroscopic data with an authentic sample of amide **324** confirmed its presence.

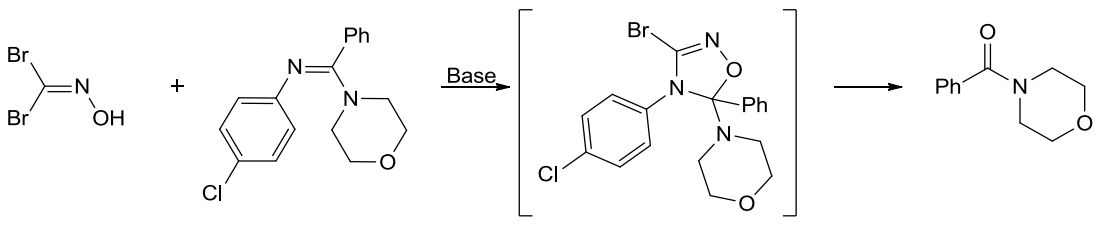


349

Figure 99: Amidine 349

4.2.3 Reactions with *N*-(*p*-chlorophenyl)-benzimidoylmorpholine

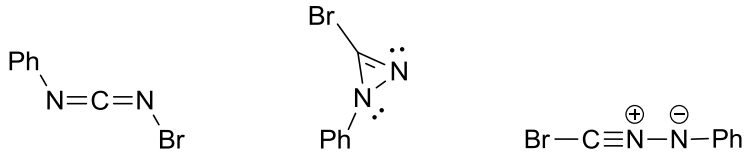
The introduction of a more electron-withdrawing substituent at the N-4 of the oxadiazoline ring was explored in an effort to stabilise the oxadiazoline formed in the 1,3-dipolar cycloaddition reaction with dibromoformaldoxime **41** as the hydroximoyl halide precursor. The reaction of dibromoformaldoxime **41** with *N*-(*p*-chlorophenyl)-benzimidoylmorpholine **353** for the attempted preparation of oxadiazoline **417** is outlined in Scheme 235.



41 **353** **417** **322**

Scheme 235: The attempted preparation of oxadiazoline 417

Irrespective of the base employed, triethylamine or potassium *t*-butoxide, the spectroscopic data obtained from these reaction mixtures demonstrate that *N*-benzoylmorpholine **322** was one of the products of the reaction. Identification of the amide **322** was facilitated by comparison with the 1H NMR spectrum of an authentic sample.Other products were not isolated nor identified but could, in line with earlier observations be the *N*-bromocarbodiimide **408**, the diarizine **410** or its ring opened isomer, the nitrile imine **411** (Figure 100).

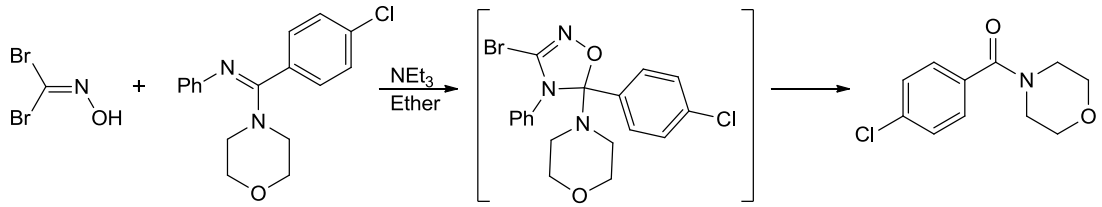


408 **410** **411**

Figure 100: The potential side products from the reaction of 41 with 353

4.2.4 Reactions with *N*-phenyl-(*p*-chlorobenzimidoyl)-morpholine

The reaction of dibromoformaldoxime **41** with *N*-phenyl-(*p*-chlorobenzimidoyl)-morpholine **357** as a preparation of oxadiazoline **418** is illustrated in Scheme 236. Introducing an electron-withdrawing *p*-chlorophenyl substituent on the amidine **357** could potentially increase the thermal stability of the oxadiazoline formed, allowing NMR spectroscopic analysis of the conversion products as they formed.



41 **357** **418** **327**

Scheme 236: The reaction of dibromoformaldoxime 41 with *N*-phenyl-(*p*-chlorobenzimidoyl)-morpholine 357

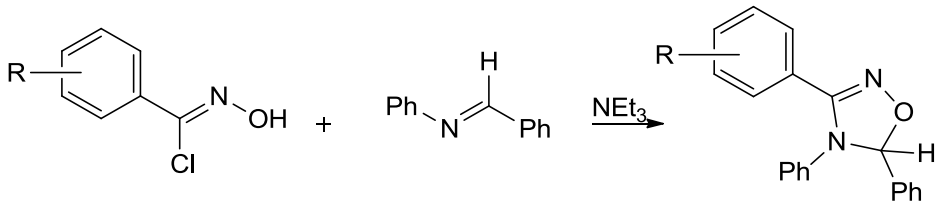
Comprison of the ^{1}H NMR spectrum of the reaction products with an authentic sample of the amide **327** confirmed that it was isolated following the cycloaddition reaction, i.e. a consistent outcome pattern for a range of benzamidines with the bromonitrile oxide.

4.3 1,3-Dipolar cycloaddition reactions with other dipolarophiles

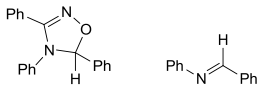
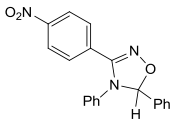
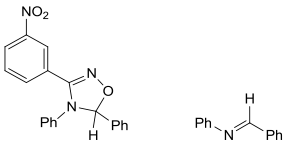
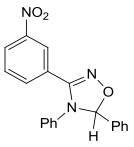
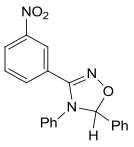
4.3.1 1,3-Dipolar cycloaddition reactions with imines

The 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from hydroximoyl halide precursors, with *N*-benzylideneaniline **346** is outlined in the following section. The results of the 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from substituted benzohydroximoyl halide precursors, with *N*-benzylideneaniline **346** at an addition temperature of less than 10 ^{o}C and triethylamine as the base are summarised in Table 36.

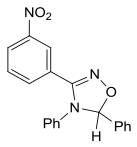
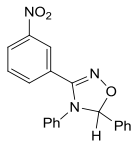
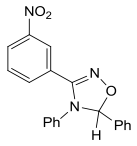
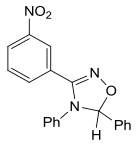
Table 36: The results of the 1,3-dipolar cycloaddition reaction of 1,3-dipoles with *N*-benzylideneaniline 346



346

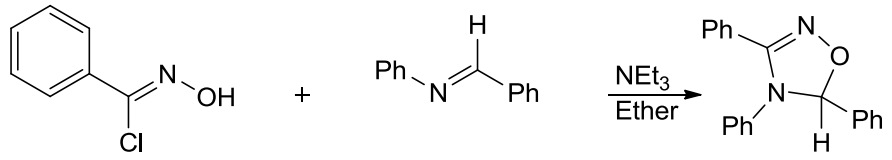
Entry	Precursor	R	Solvent	Stir time	Isolation method[21]	Product(s)
1	**26**	H-	Ether	12 h	B	 **419** **346** (80 : 20)
2	**275**	*p*-NO_2-	Ether	10 min	A	 **420** 60%
3	**276**	*m*-NO_2-	Ether	16.25 h	B	 **421** **346** (78 : 22)
4	**276**	*m*-NO_2-	DCM	10 min	A	 **421** 40%
5	**276**	*m*-NO_2-	DCM	1 h	A	 **421** 85%

[21] Method A indicates an aqueous work up, method B indicates isolation by filtration.

Entry	Precursor	R	Solvent	Stir time	Isolation method[22]	Product(s)
6	**276**	*m*-NO_2-	DCM	6 h	B	 **421** 48%
7	**276**	*m*-NO_2-	Ether	10 min	B	 **421** 67%
8	**276**	*m*-NO_2-	Ether	1 h	B	 **421** 73%
9	**276**	*m*-NO_2-	Ether	6 h	B	 **421** 27%

Entry 1 in Table 36 shows the synthesis of oxadiazoline **419** from benzohydroximoyl chloride **26** and imine **346** (Scheme 237). The spectroscopic data of the oxadiazoline **419** correlates to that in the literature with the 5-H proton NMR spectroscopy resonance of **419** observed at 6.54 ppm.[196] Aitken *et al.* found that the oxadiazoline '*^{1}H signal for the 5-H generally appearing as a singlet in the range δ_H 6.3-6.6 and the ^{13}C spectra forming a highly consistent pattern with signals for C3 at δ_C 154-159 and for C5 at δ_C 90-100*'.

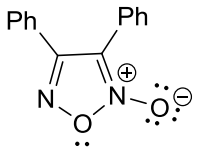
[22] Method A indicates an aqueous work up, method B indicates isolation by filtration.



26 **346** **419**

Scheme 237: The synthesis of oxadiazoline 419

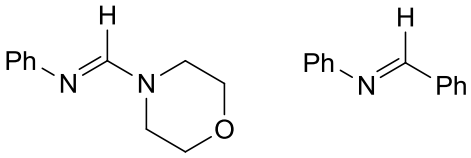
As the ^{1}H NMR spectroscopic signals of the oxadiazoline **419** and the imine **346** are both evident in the spectra, it may be concluded that stirring the reaction mixture overnight was not long enough to bring the cycloaddition to completion. However, the proton NMR spectroscopic data of the aromatic signals in the oxadiazoline **419** and imine **346** would mask any furoxan **422** (Figure 101) signals which may also account for the reason why the cycloaddition did not appear to go to completion within the timeframe examined.



422

Figure 101: The structure of 3,4-diphenylfuroxan 422

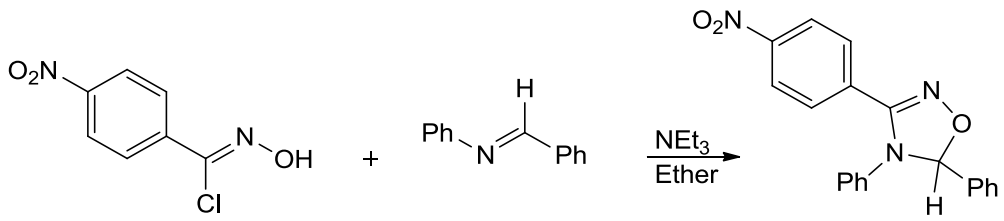
On comparison with formamidine **341**, the imine **346** reacts slower with the 1,3-dipole. This could be due to the conjugation of the N=C bond in the formamidine with the lone pair of electrons on the nitrogen of the C-N bond of the secondary amine group (Figure 102).



341 **346**

Figure 102: The structure of imine 346 and amidine 341

Inserting a *p*-nitrophenyl substituent into the C-3 position of the oxadiazoline (Entry 2, Table 36) was achieved by the reaction of *p*-nitrobenzohydroximoyl chloride **275** with imine **346** (Scheme 238). Recrystallisation of the product from ethyl acetate - hexane gave the oxadiazoline **420** in 60% yield. Its melting point (143-144 ^{o}C) is in excellent correlation with the literature.[204]



275 **346** **420**

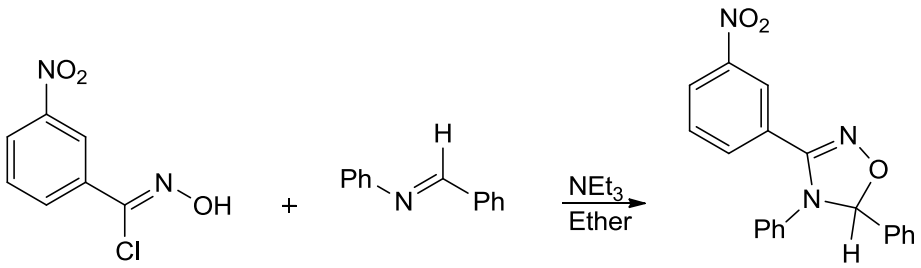
Scheme 238: The reaction of 275 with imine 346

The formation of the oxadiazoline **420** was confirmed by the presence of the oxadiazoline proton signal at 6.55 ppm in the ^{1}H NMR spectroscopic analysis. The spectroscopic data correlates well with the structure and its assignment was aided by HMBC and HSQC experiments (Table 37).

Table 37: The ^{13}C NMR spectroscopic data of 420

$\delta_{C\ (ppm)}$	
N<u>C</u>HON	101.4
8 x Ar<u>C</u>H	123.9, 124.6, 126.5, 128.8, 128.9 and 130.1
ArC(NO_2)	131.8
***ipso* <u>C</u> of Ar at C_5 of oxadiazoline**	138.4
***ipso* <u>C</u> of Ar at N_4 of oxadiazoline**	140.7
***ipso* <u>C</u> of Ar at C_3 of oxadiazoline**	148.9
N<u>C</u>(*p*-NO_2Ar)=N	153.8

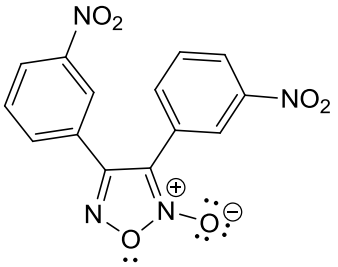
Reactions involving *m*-nitrobenzohydroximoyl chloride **276** and imine **346** in the preparation of oxadiazoline **421** are summarised by Entries 3-9 in Table 36 (Scheme 239). The initial reaction protocol involved stirring the reagents for 16.25 h and isolating the reaction product by filtration.



276 **346** **421**

Scheme 239: The preparation of oxadiazoline 421 by the reaction of *m*-nitrobenzohydroximoyl chloride 276 and imine 346 in the presence of base

This resulted in a mixture of oxadiazoline **421** and imine **346** following an attempted recrystallization from chloroform - hexane. The H-5 oxadiazoline proton NMR spectroscopy singlet was observed at 6.56 ppm. The ratio of oxadiazoline to imine illustrates that even after 16.25 h of stirring the reaction mixture, the cycloaddition did not go to completion. However, the proton NMR spectroscopic data of the aromatic signals in the oxadiazoline **421** and imine **346** would mask any furoxan **423** signals which may also account for the reason why the cycloaddition did not appear to go to completion within the timeframe examined (Figure 103).



423

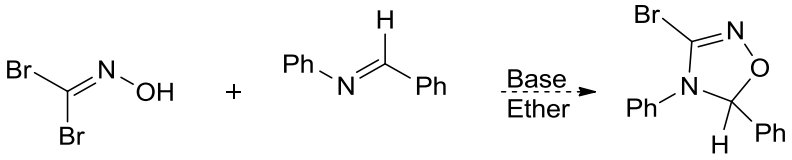
Figure 103: The structure of furoxan 423

Whether the oxadiazoline **421** could be formed within ten minutes of stirring the reagents was then investigated (Entry 4). Following an aqueous work-up, the compound **421** was isolated in 85% yield as a yellow oil. Its spectroscopic data is in excellent correlation with the structure. HRMS analysis confirmed the elemental composition of the oxadiazoline. Further variation of the reaction stir time, the method of isolation or changing the solvent from dichloromethane (Entry 6) to ether (Entry 9) did little to improve the yield or the outcome of the cycloaddition. In all cases, evidence for the oxadiazoline **421** was observed, but the compound was not isolated.

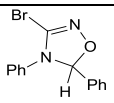
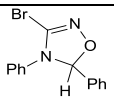
In relation to aromatic nitrile oxides, '*the rate of dimerization depends on the nature of the substituent on the aromatic ring*'-Lowe *et al*.[52] They investigated having a nitro group on the aromatic ring of the nitrile oxide and the effect it would exert on the nitrile oxide stability. '*to ascertain the influence of the electrical nature of the nitro group and the effect of its position on the addition reaction*.' The Hammett σ constants for *m*-nitro (+0.71) and *p*-nitro (+0.78) substituents are similar so one would predict that the nitrile oxides should react in a similar manner. Our experimental results support this position.

The results of the 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from a dihaloformaldoxime precursor, with *N*-benzylideneaniline **346** at an addition temperature of less than 10 °C are summarised in Table 38.

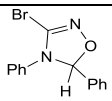
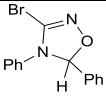
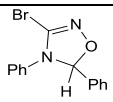
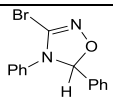
Table 38: The 1,3-dipolar cycloaddition reactions of dibromoformaldoxime 41 with *N*-benzylideneaniline 346



41 **346** **424**

Entry	Base	Stir time	Product(s)
1	^{t}BuOK	15 h	 **424**  **346**  **270** (14 : 69 : 17).
2	NEt_3	0 min[23]	 **424**  **346**  **270** (3 : 88 : 9)

[23] 0 min stir time refers to the reaction mixture being filtered immediately once the addition of the dihalformaldoxime solution had been completed.

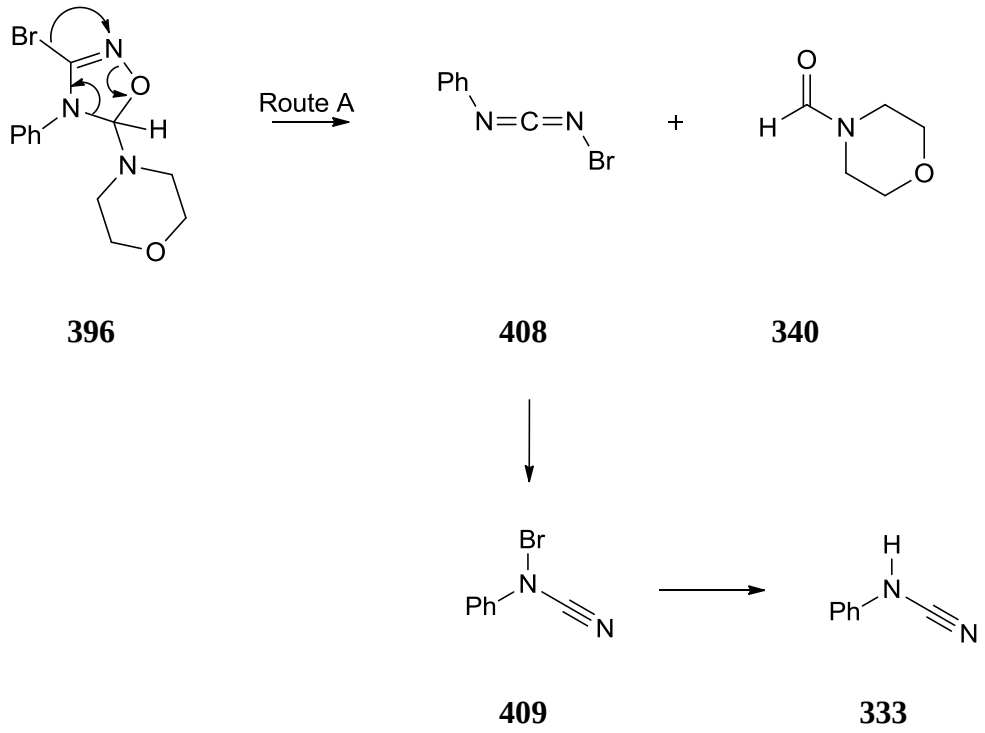
Entry	Base	Stir time	Product(s)
3	NEt_3	0 min[24]	 **424**  **346**  **270** (3 : 90 : 7)
4	NEt_3	1 h	 **424**  **346**  **270** (2 : 93 : 5)
5	NEt_3	6 h	 **424**  **346**  **270** (2 : 84 : 14)
6	NEt_3	19.5 h	 **424**  **346**  **270** (2 : 75 : 23)

The initial reaction conditions used potassium *t*-butoxide and a stir time of 15 h (Entry 1, Table 38). NMR spectroscopic analysis of the reaction mixture showed the presence of oxadiazoline **424**, imine **346** and aldehyde **270** in the ratio of 14 : 69 : 17. Comparison of the NMR spectra with the literature data confirmed the presence of benzaldehyde.[205] The mass spectral analysis confirmed the presence of bromine in the heterocycle. The stir time of the reaction did not appear to have a significant effect on the formation of the oxadiazoline **424**. Increasing that variable from 0 min to 19.5 h did not directly impact the yield of oxadiazoline formed (Entry 6, Table 38). The amount of benzaldehyde present increased as the stir time was increased. Benzaldehyde can be a contaminant in the imine sample, being carried through in the imine synthesis. However, NMR spectroscopic analysis carried out prior to the cycloaddition reaction showed that only a very small trace of benzaldehyde was present in the imine sample. This raised the question of whether the benzaldehyde is a product of the cycloaddition reaction or originates from hydrolysis of the imine. An attempt to isolate a sample of the oxadiazoline **424** by column chromatography was unsuccessful. Thus, the thermal stability of the oxadiazoline **424** is called into question. The use of triethylamine *versus* potassium *t*-butoxide shows that potassium *t*-butoxide gave the oxadiazoline **424** in a greater yield than all of the reactions involving triethylamine. The formation of the

[24] 0 min stir time refers to the reaction mixture being filtered immediately once the addition of the dihalformaldoxime solution had been completed.

oxadiazoline **424** was confirmed by the presence of the oxadiazoline proton signal at 6.50 ppm in the ^{1}H NMR spectroscopic analysis.

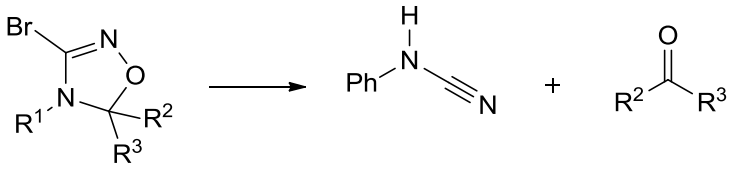
Clearly, bromine as a substituent at the 3-position of the putative cycloadducts derived from a range of amidines induces a significant change in the reactivity of the heterocycle. Following the putative reaction mechanism discussed earlier in this chapter, route A indicates that phenylcyanamide **333** could have formed from the attempted synthesis of oxadiazoline **396** (Scheme 240).



Scheme 240: Putative route A mechanism of decomposition of oxadiazoline 396

Table 39 summarises the results of the cycloaddition reactions with dibromoformaldoxime and interestingly, an amide decomposition product rather than a urea is evident for a range of compounds.

Table 39: The results of the attempted synthesis of 3-bromo-Δ^2-1,2,4-oxadiazoline



333

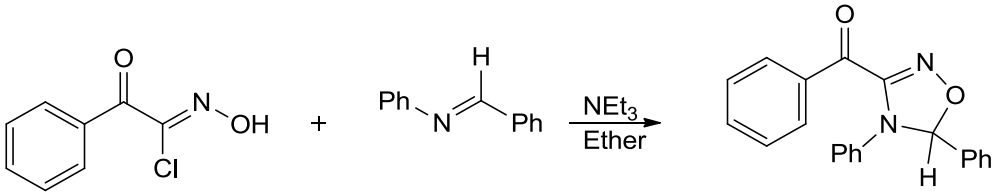
Entry	Oxadiazoline	R^1	R^2	R^3	Amide	Phenylcyanamide[25] 333
1	**370**	$PhCH_2$-	-$N(CH_3)_2$	H	**371**	Not observed
2	**385**	$PhCH_2$-	Morpholino-	H	**340**	Not observed
3	**396**	Ph-	Morpholino-	H	**340**	**333**
4	**407**	Ph-	Morpholino-	Ph	**322**	Not observed
5	**414**	Ph-	Piperidino-	Ph	**324**	Not observed
6	**417**	*p*-ClC_6H_4-	Morpholino-	Ph	**322**	Not observed
7	**418**	Ph-	Morpholino-	*p*-ClC_6H_4-	**327**	Not observed
8	**424**	Ph-	Ph-	H	**270**	Not observed

Decomposition to a mixture of nitrile and urea involving a hydrogen atom migration is superseded by a cyanamide/heterocumulene and amide route, a process that we have described earlier in this thesis as the imidoyl nitrene route (Scheme 232). This route seems to prevail regardless of hydrogen or an aryl group as a substituent at the C-5 position of the oxadiazoline intermediate.

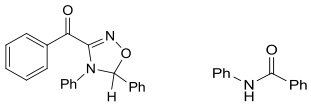
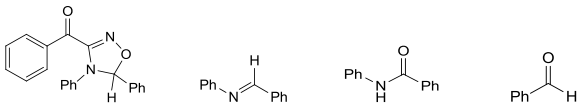
The results of the 1,3-dipolar cycloaddition reaction of 1,3-dipoles, from a 1-aroyl-1-chloroformaldoxime precursor, with *N*-benzylideneaniline **346** at an addition temperature of less than 10 ^oC are summarised in Table 40.

[25] The term 'Not observed' is used when an absorption corresponding to the cyano group in phenylcyanamide is not observed.

Table 40: The 1,3-dipolar cycloaddition reaction of 1,3-dipoleswith *N*-benzylideneaniline 346



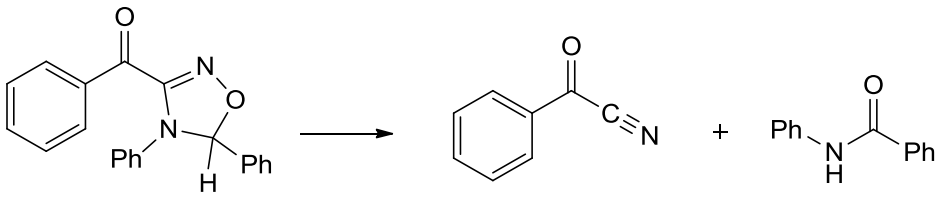
286 **346** **425**

Entry	Stir time	Isolation method[26]	Product(s)
1	3 h	A	 **425** **347** (50 : 50)
2	15 h	B	 **425** **346** **347** **270** (38 : 48 : ?[27] : 14)

The reaction of 1-benzoyl-1-chloroformaldoxime **286** with imine **346** is outlined in entries 1-2 in Table 40. Utilising a 3 h stir time and recrystallisation from ethyl acetate - hexane yielded a 1 : 1 mixture of the oxadiazoline **425** and amide **347** (Entry 1). The formation of the oxadiazoline **425** was confirmed by the presence of the oxadiazoline proton signal at 6.61 ppm in the ^{1}H NMR spectroscopic analysis. The amide (benzanilide) **347** may have originated from the oxadiazoline **425** through the imidoyl nitrene pathway – see Scheme 233. The presence of the benzoyl group at the C-3 position of the oxadiazoline, combined with phenyl groups at N_4 and C_5 should serve to stabilise the ring structure. However, detection of an amide product conflicts with this expectation. Increasing the stir time to 15 h, gave a crude reaction mixture of products - oxadiazoline **425**, imine **346**, amide **347** and aldehyde **270** in a ratio of 37 : 48 : ?[28] : 14 (Entry 2, Table 40). With both results, an argument for the presence of the nitrile exists. If conversion is taking place, then the nitrile **387** and amide **347** will be present in equal quantities (Scheme 241). Al-Awadi *et al.* describe benzoyl cyanide **387** as showing a 3H proton NMR spectroscopy multiplet at 7.25-7.83 ppm and a 2H proton NMR

[26] Method A indicates an aqueous work up, method B indicates isolation by filtration.
[27] ? indicates that amide **347** was unquantifiable in ^{1}H NMR spectrum.
[28] ? indicates that amide **347** was unquantifiable in ^{1}H NMR spectrum.

spectroscopy multiplet at 8.00-8.67 ppm.[202] The proton NMR spectrum of the product mixture from reaction of **286** with **346** showed extra peaks in the aromatic region of which signals at 7.47 and 7.87 ppm could be representative of the nitrile. It is worth noting that the 1,3-dipolar cycloaddition reaction appears to take longer for completion when an imine is the dipolarophile.

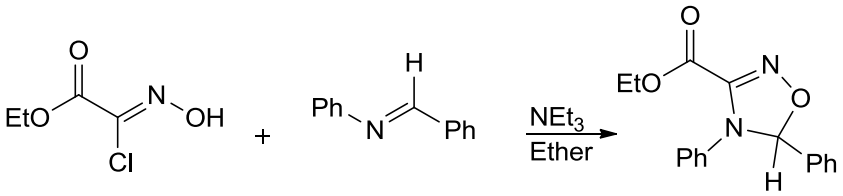


425 **387** **347**

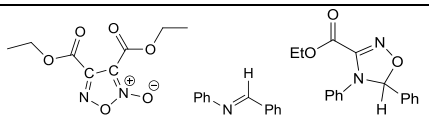
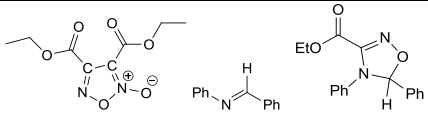
Scheme 241: The cycloreversion of oxadiazoline 425

Table 41 outlines the 1,3-dipolar cycloaddition reaction of ethylchloroglyoxalate oxime **295** with *N*-benzylideneaniline **346** at an addition temperature of less than 10°C.

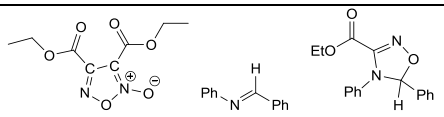
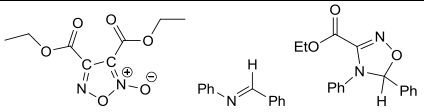
Table 41: The effect of varying the stir time and isolation method in the 1,3-dipolar cycloaddition reaction of 295 with 346



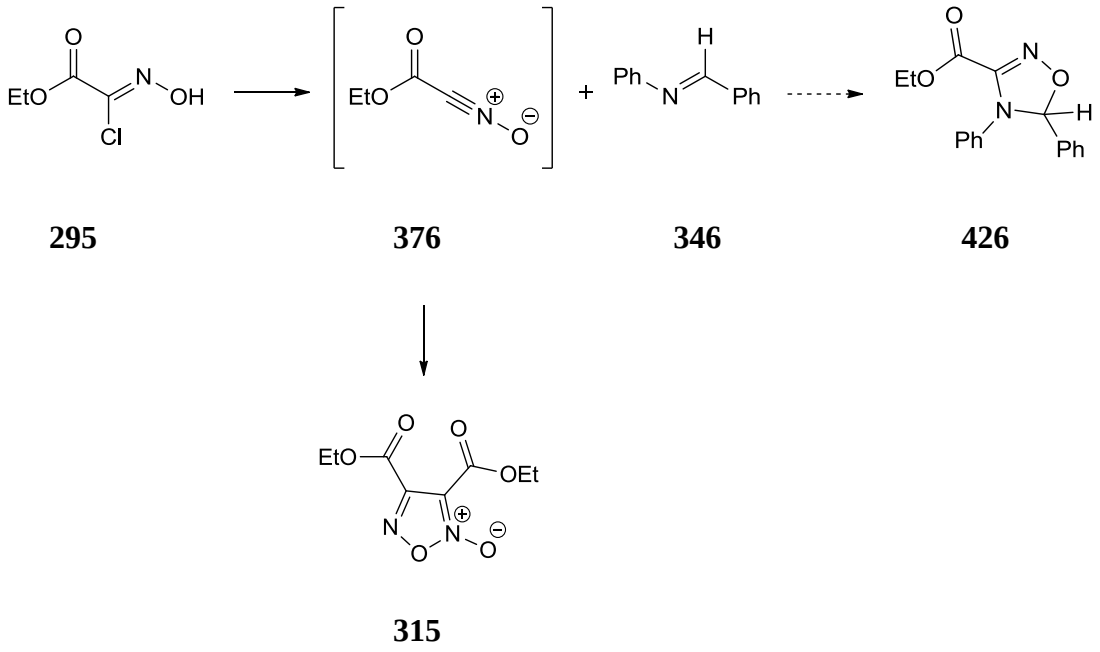
295 **346** **426**

Entry	Stir time	Isolation method[29]	Product(s)
1	10 min	A	 **315** **346** **426** (31 : 63 : 6)
2	3 h	A	 **315** **346** **426** (31 : 63 : 6)

[29] Method A indicates an aqueous work up, method B indicates isolation by filtration.

Entry	Stir time	Isolation method[30]	Product(s)
3	12.5 h - syringe pump addition	B	 **315** **346** **426** (28 : 55 : 17)
4	< 10 °C for 2.5 h, then 20 °C 12 h	B	 **315** **346** **426** (25 : 50 : 25)

Whether the reagents were stirred together for 10 min or 3 h (Entries 1 and 2), the reaction outcome was the same; the oxadiazoline **426**, furoxan **315** and imine **346** were isolated as a mixture in a ratio of 6 : 31 : 63 (Scheme 242).



295 **376** **346** **426**

315

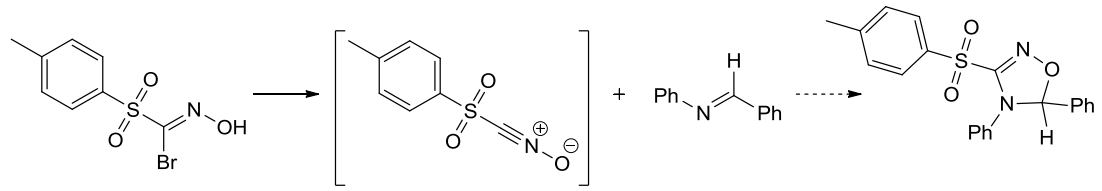
Scheme 242: The attempted synthesis of oxadiazoline 426

Changing the rate of addition was believed to benefit the formation of oxadiazoline **426** if the nitrile oxide **376** was tending towards dimerisation rather than adding to the dipolarophile. Kamimura *et al.* used a syringe pump to add the nitrile oxide precursor slowly to a solution of dipolarophile (over 12 h) to avoid dimerization of the nitrile oxide.[12z] Incorporating the use of a syringe pump for addition of a solution of ethylchloroglyoxalate oxime **295** in ether served to add the hydroximoyl halide solution at a rate of 0.793 mL/h. This did increase the

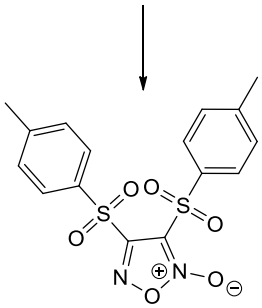
[30] Method A indicates an aqueous work up, method B indicates isolation by filtration.

yield of oxadiazoline **426** formed, but the ratio of oxadiazoline : furoxan : imine was relatively unchanged (Entry 3, Table 41). Kozikowski *et al.* noted the use of a syringe pump during the 1,3-dipolar cycloaddition reaction of ethylchloroglyoxalate oxime **295** to an alkene.[157] They added the base *via* syringe pump rather than the hydroximoyl halide. When we added the base *via* syringe pump to a stirring solution of ethylchloroglyoxalate oxime **295** and imine **346**, the overall proportion of oxadiazoline **426** improved to a ratio of 1 : 1 : 2 relative to the imine and dimer (Entry 4, Table 41). The key proton NMR spectroscopy signals for imine (8.45 ppm), oxadiazoline (6.50 ppm) and furoxan (4.45 ppm) were used to identify the compounds.

The 1,3-dipolar cycloaddition reaction of 1-*p*-toluenesulfonyl-1-bromoformaldoxime **299** with imine **346** in the presence of triethylamine at an addition temperature of less than 10°C was next undertaken (Scheme 243).The reaction mixture was stirred overnight and a mixture of products was isolated. The oxadiazoline **427**, imine **346**, amide **347**, aldehyde **270** and furoxan **309** were isolated as a mixture in a ratio of 4 : 29 : ?[31] : 44 : 23. The formation of the oxadiazoline **427** was confirmed by the presence of the oxadiazoline proton signal at 6.56 ppm in the ^{1}H NMR spectroscopic analysis.



299 **307** **346** **427**



309

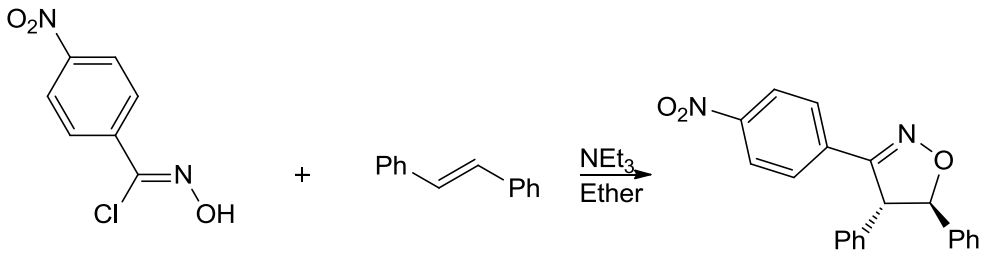
Scheme 243: The attempted synthesis of oxadiazoline 427

[31]? indicates that amide **347** was unquantifiable in ^{1}H NMR spectrum.

In relation to the 1,3-dipolar cycloaddition reaction of benzenesulfonylnitrile oxide with alkenes, Wade *et al.* stated that triethylamine could be used as the base, '*but only with the more reactive alkenes*'.[51b] They found that the major product of the reaction of benzenesulfonylnitrile oxide with an alkene was the nitrile oxide dimer.

4.3.2 1,3-Dipolar cycloaddition reactions with an alkene

The reaction of *p*-nitrobenzohydroximoyl chloride **275** with *trans*-stilbene **428** in the presence of triethylamine at an addition temperature of less than 10°C was next undertaken (Scheme 244). The ^{1}H NMR spectrum for the crude reaction mixture showed evidence for the isoxazoline **429** and *trans*-stillbene **428**. Recrystallisation from chloroform - hexane gave the isoxazoline as an orange solid in 13% yield. Further purification by column chromatography was unsuccessful as the compound degraded to unknown products.



275 **428** **429**

Scheme 244: The attempted synthesis of isoxazoline 429

4.4 NMR spectroscopy tube experiments

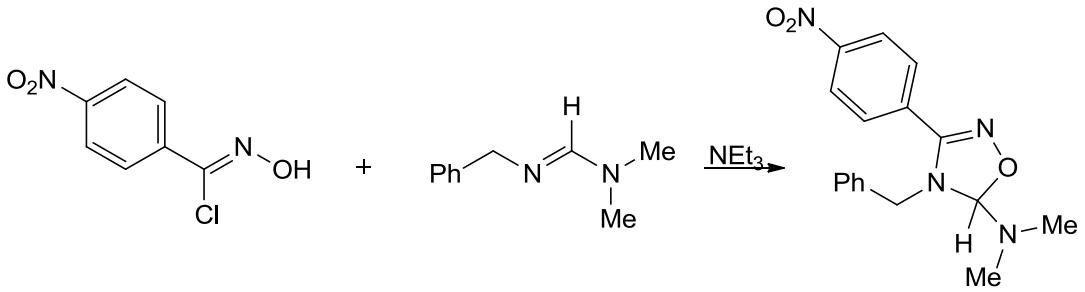
In the expectation that a nitrile oxide was relatively stable and its kinetics for reaction with amidines could be measured, we examined the progress of the 1,3-dipolar cycloaddition reaction in an NMR spectroscopy tube in $CDCl_3$. Initially, the nitrile oxide was generated *in situ* by reaction of a base with the hydroximoyl halide precursor. This gave rise to a partial precipitate of triethylamine hydrochloride with accompanying evidence for the triethylamine hydrochloride salt in the proton NMR spectrum. One way to avoid the extra signals in the NMR spectroscopic analysis was to use freshly generated nitrile oxide and to add this to the amidine. In some cases this was very beneficial as it gave a clear indication of the conversion to the oxadiazoline. However, in other cases the nitrile oxide proved to be too reactive and favoured the formation of the corresponding furoxan.

Time was initially a factor to be considered in carrying out NMR spectroscopy tube reactions. We wanted to establish the timeframe in which the oxadiazoline was being produced.

Previous work carried out by D. Hogan suggested that the oxadiazoline was forming within minutes of stirring the starting materials in synthetic scale reactions.[140]

The NMR spectroscopy reactions were set up so that a nitrile oxide formation check would take place first. This involved establishing that dehydrohalogenation had taken place and a check to see if dimerisation of the nitrile oxide had occurred prior its combination with the dipolarophile. A portion of the combined solution was then submitted for ^{1}H NMR spectroscopic analysis. Typically, the ^{1}H NMR spectroscopic analysis procedure took as little as seven minutes before a spectra was available to view. Subsequent NMR spectra were measured in order to follow the reaction as it progressed to oxadiazoline and in some cases until secondary reactions had occurred.

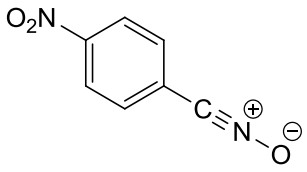
The NMR spectroscopy tube reaction of *p*-nitrobenzohydroximoyl chloride **275** with amidine **339** (Figure 105) was examined first (Scheme 245). The aim of the experiment was to ascertain the rate of formation of oxadiazoline **367**.



275 **339** **367**

Scheme 245: The reaction of *p*-nitrobenzohydroximoyl chloride 275 with amidine 339

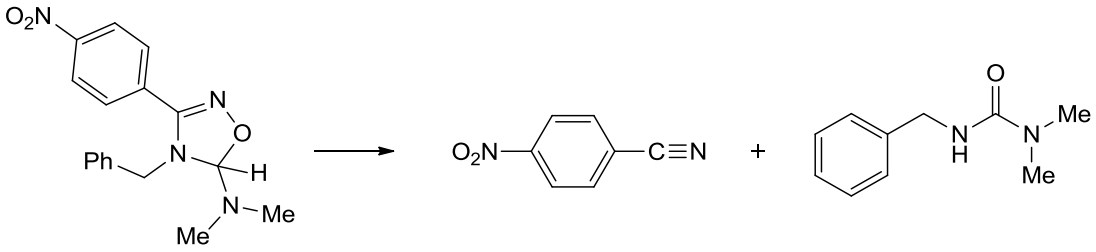
The ^{1}H NMR spectroscopic analysis of the first experiment (Figure 105-i) shows immediate conversion of the hydroximoyl chloride **275** to the nitrile oxide **265** in the presence of triethylamine (Figure 104). On mixing with the dipolarophile **339** (Figure 105-ii), the oxadiazoline **367** immediately formed (observed 9 min after the addition of the dipolarophile **339**).



265

Figure 104: Nitrile oxide 265

The reaction was monitored at intervals and decomposition of the oxadiazoline began within 21 h (Figure 105-iv) to form the corresponding nitrile **378** and urea **335** (Scheme 246).



367 **378** **335**

Scheme 246: The decomposition of the oxadiazoline 367 to form the nitrile 378 and urea 335

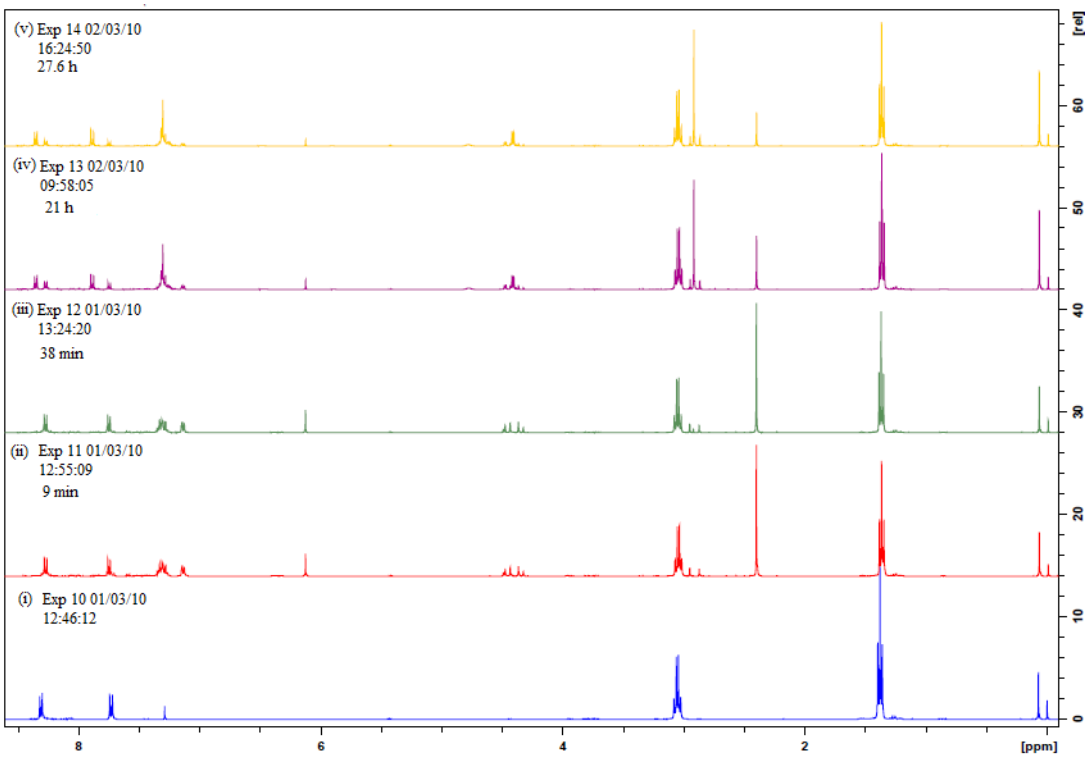
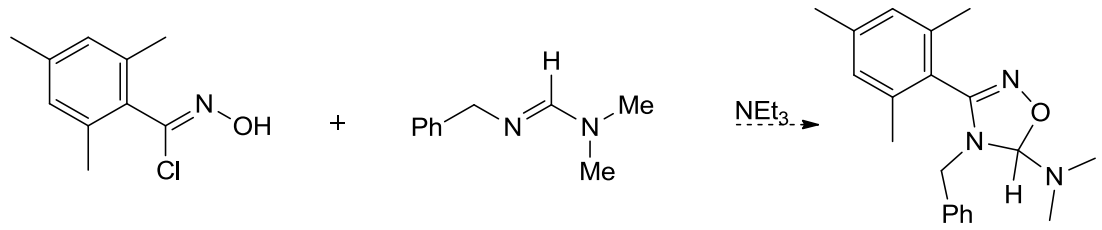


Figure 105: The ^{1}H NMR spectroscopy tube reaction of *p*-nitrobenzohydroximoyl chloride 275 with amidine 339 in $CDCl_3$ at 300K over 27 h

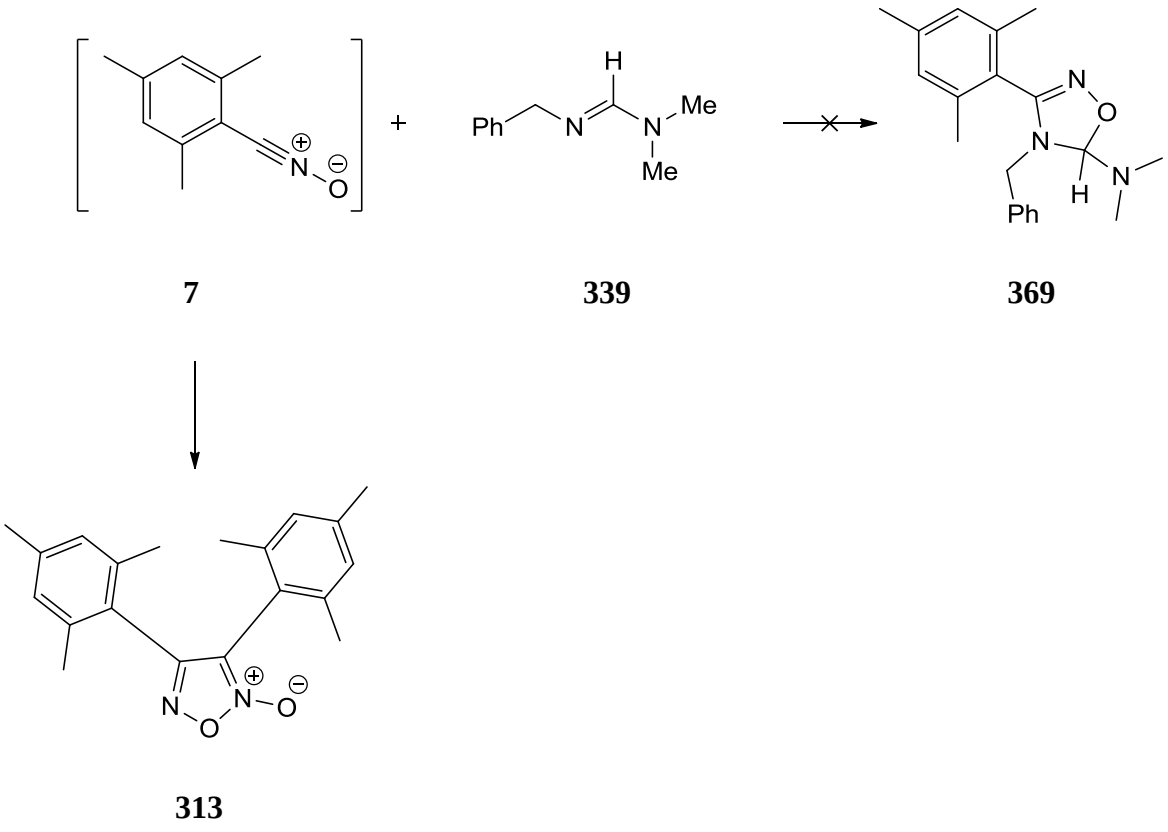
The reaction of 2,4,6-trimethylbenzohydroximoyl chloride **281** with amidine **339** was monitored by ^{1}H NMR spectroscopy (Scheme 247).



281 **339** **369**

Scheme 247: The reaction of 2,4,6-trimethylbenzohydroximoyl chloride 281 with amidine 339

Following the addition of reagents, the reaction was monitored over 17 h. It showed that the cycloaddition reaction did not take place within 17 h of combining the reactants as indicated by the presence of mesitonitrile-*N*-oxide **7** (2.30 and 2.42 ppm) and *N*,*N*-dimethyl-*N´*-benzylformamidine **339** (7.38 ppm). A second attempt at promoting formation of oxadiazoline was carried out by the reaction of mesitonitrile-*N*-oxide **7** with the amidine **339** over a longer period of reaction time (Scheme 248). ^{1}H NMR spectroscopic analysis suggested that the nitrile oxide **7** and amidine **339** did not undergo any cycloaddition reaction; the furoxan **313** was observed to have formed after 65 h. The amidine **339** appears to have degraded over this time.

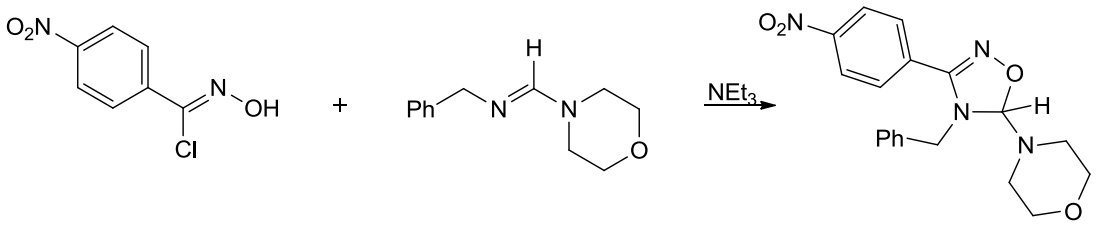


7 **339** **369**

313

Scheme 248: The conversion of mesitonitrile-*N*-oxide 7 to dimesitylfuroxan 313

The NMR spectroscopy tube experiments involving the interaction of hydroximoyl halides with *N*-benzylformimidoylmorpholine **318** were examined (Scheme 249). *p*-Nitrobenzohydroximoyl chloride **275** and *N*-benzyl amidine **318** were reacted together with triethylamine in an NMR spectroscopy tube and the reaction was monitored by ^{1}H NMR spectroscopy.

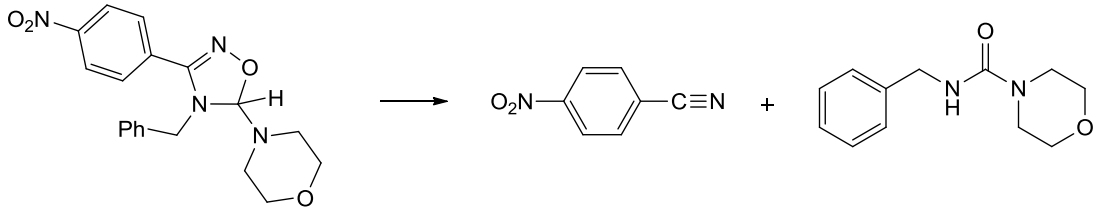


275 **318** **381**

Scheme 249: The reaction of *p*-nitrobenzohydroximoyl chloride 275 and *N*-benzyl amidine 318

The oxadiazoline **381** formed quantitatively on mixing of reactants. Following 4.75 h, conversion of oxadiazoline **381** to the nitrile **378** and urea **336** began to occur and they were produced in a 50:50 ratio (Scheme 250). Comparison with an authentic sample of the urea **336**

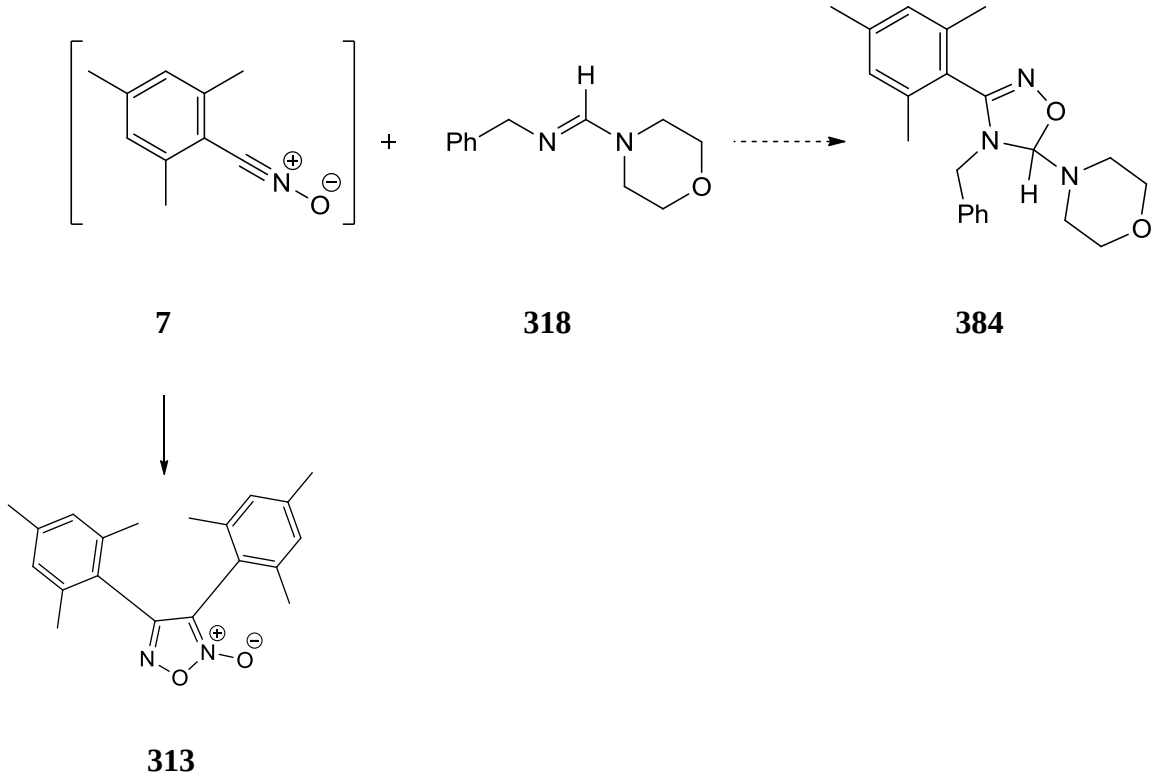
and with literature data of the nitrile confirmed their identity. The transformation was complete in 128 h.[206]



381 **378** **336**

Scheme 250: The cycloreversion of oxadiazoline 381 to nitrile 378 and urea 336

Monitoring the reaction of mesitonitrile-*N*-oxide **7** with amidine **318** showed that the oxadiazoline **384** did not form and that the nitrile oxide dimerised to furoxan **313** in the presence of **318** (Scheme 251). The reaction was monitored for 360.8 h.



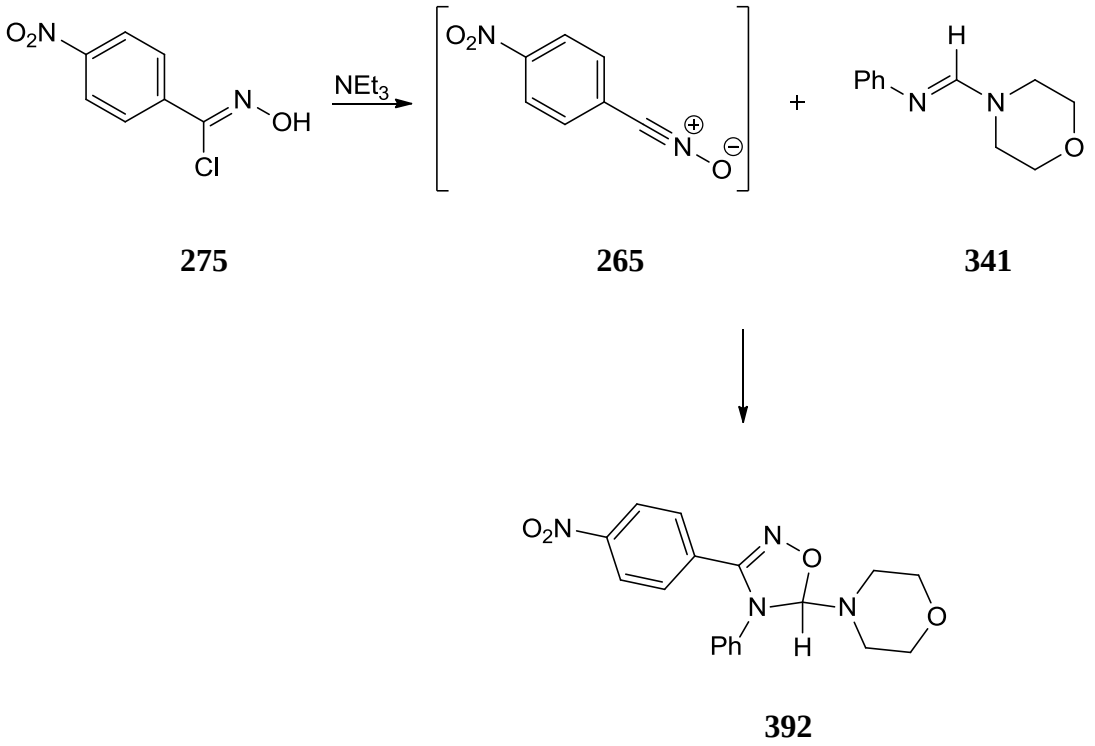
7 **318** **384**

313

Scheme 251: The reaction of mesitonitrile-*N*-oxide 7 with amidine 318

The NMR spectroscopy tube experiments involving the interaction of hydroximoyl halides with *N*-phenylformimidoylmorpholine **341** were examined (Scheme 252). The NMR spectroscopy tube reaction of *p*-nitrobenzohydroximoyl chloride **275** with amidine **341** for the intended generation of oxadiazoline **392** showed that on reacting hydroximoyl chloride **275**

with triethylamine, the chloride was converted completely to *p*-nitrobenzonitrile-*N*-oxide **265**. Spectra recorded subsequently illustrate that while some amidine **341** is still present, all of the nitrile oxide has been consumed within 7 min to form oxadiazoline **392**.

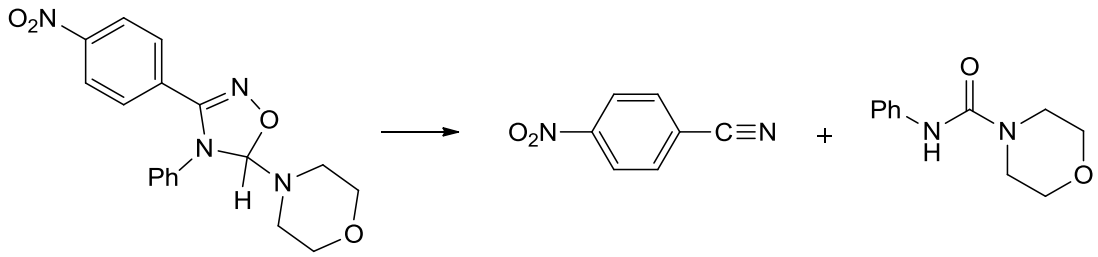


275 **265** **341**

392

Scheme 252: The reaction of *p*-nitrobenzohydroximoyl chloride 275 with amidine 341 for the intended generation of oxadiazoline

When pregenerated *p*-nitrobenzonitrile-*N*-oxide **265** was used, the oxadiazoline **392** was formed immediately. The reaction solution was monitored over 44 days for conversion to the nitrile **378** and urea **395**, but neither was evident in this timeframe (Scheme 253).

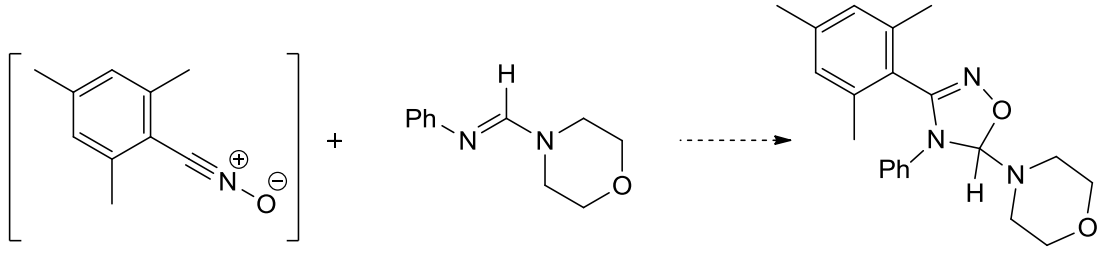


392 **378** **395**

Scheme 253: The cycloreversion of oxadiazoline 392 to nitrile 378 and urea 395

Upon reacting mesitonitrile-*N*-oxide **7** with amidine **341** for the attempted preparation of oxadiazoline **394**, NMR spectroscopic analysis showed that the sample contained the amidine **341** (7.51 ppm) and nitrile oxide **7** (2.30, 2.42 and 6.91 ppm) in a 1:1 ratio (Scheme 254).

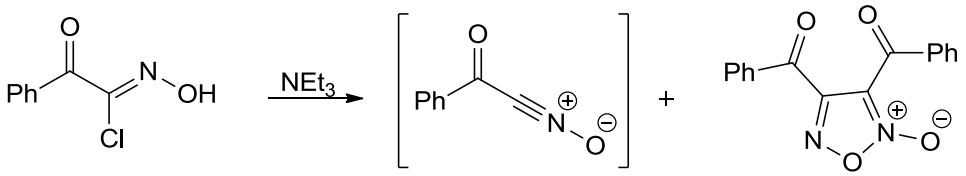
Subsequent NMR spectroscopic analysis carried out over 360 h (15 days) showed no change to the result.



7 **341** **394**

Scheme 254: The reaction of mesitonitrile-*N*-oxide 7 with amidine 341 for the attempted preparation of oxadiazoline 394

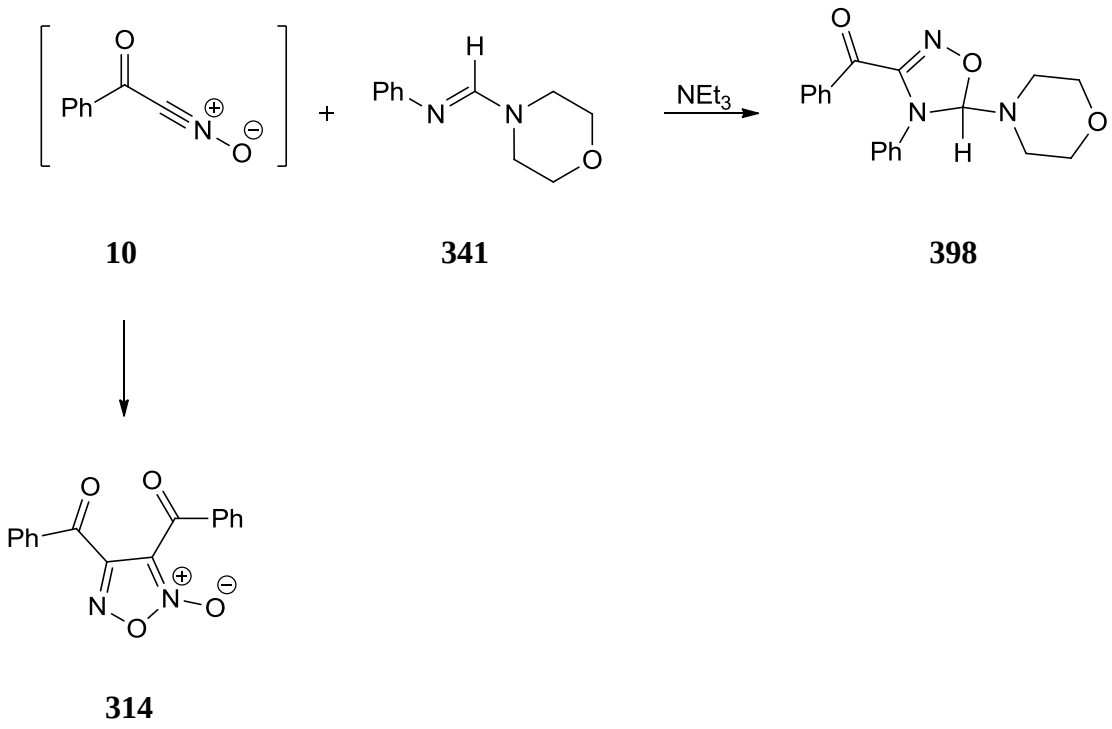
The ^{1}H NMR spectroscopy check of the reaction of 1-benzoyl-1-chloroformaldoxime **286** with triethylamine established that a 50 : 50 ratio of nitrile oxide **10** and furoxan **314** was present (Scheme 255).



286 **10** **314**

Scheme 255: The dehydrohalogenation of 286

Reaction of this solution with amidine **341** gave furoxan **314**, amidine **341** and oxadiazoline **398** in a ratio of 23 : 58 : 19 (Scheme 256). This shows that within 8 min of mixing the dipole and dipolarophile, the oxadiazoline **398** was formed. Spiking the reaction mixture with an authentic sample of the oxadiazoline **398** confirmed its presence.

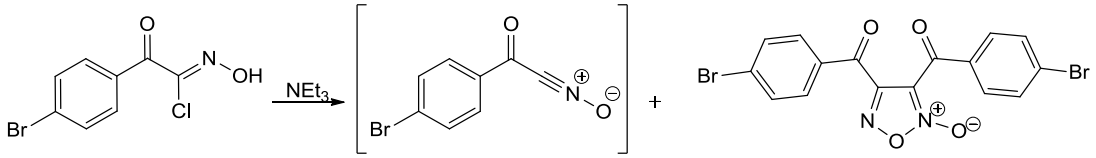


10 **341** **398**

314

Scheme 256: The reaction of with amidine 341

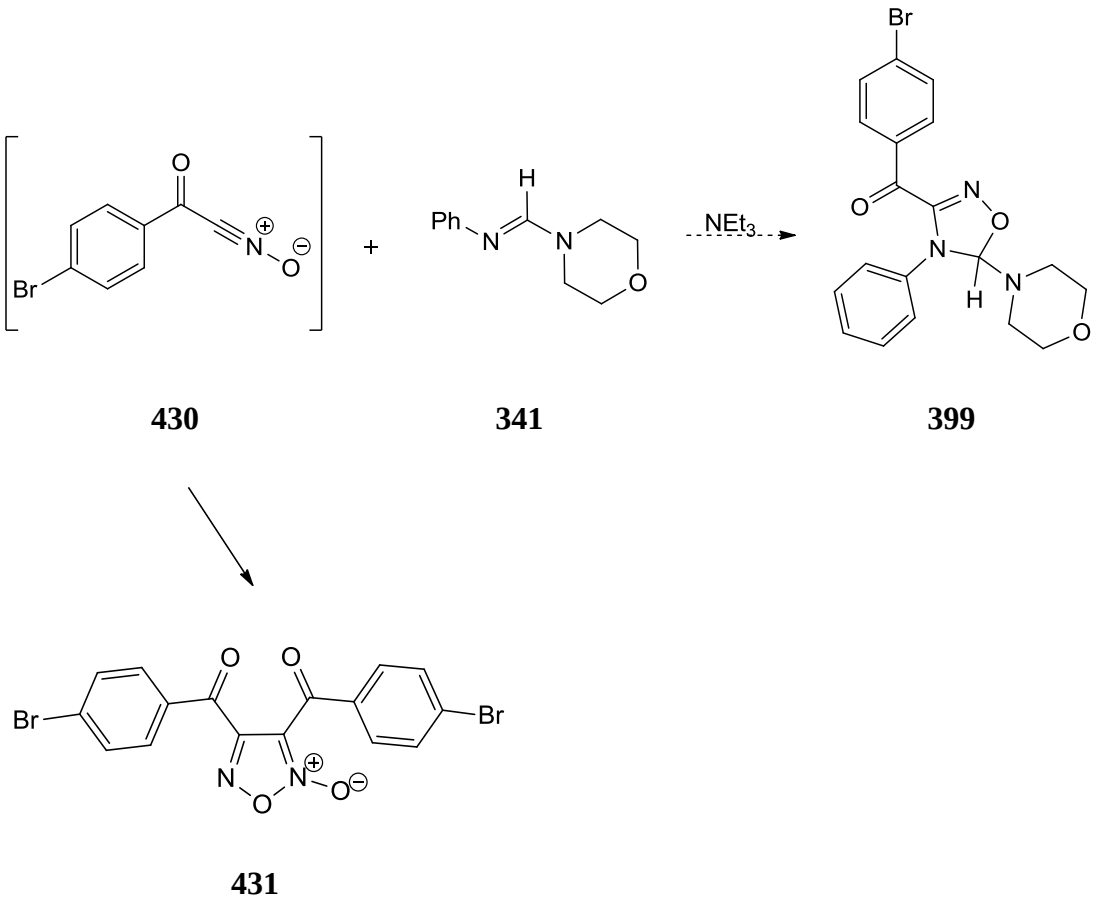
The NMR spectroscopy tube reaction of 1-(*p*-bromobenzoyl)-1-chloroformaldoxime **292** and amidine **341** illustrated that dehydrohalogenation of the hydroximoyl halide precursor gave a mixture of nitrile oxide **430** and furoxan **431** (Scheme 257).



292 **430** **431**

Scheme 257: The dehydrohalogenation of 292

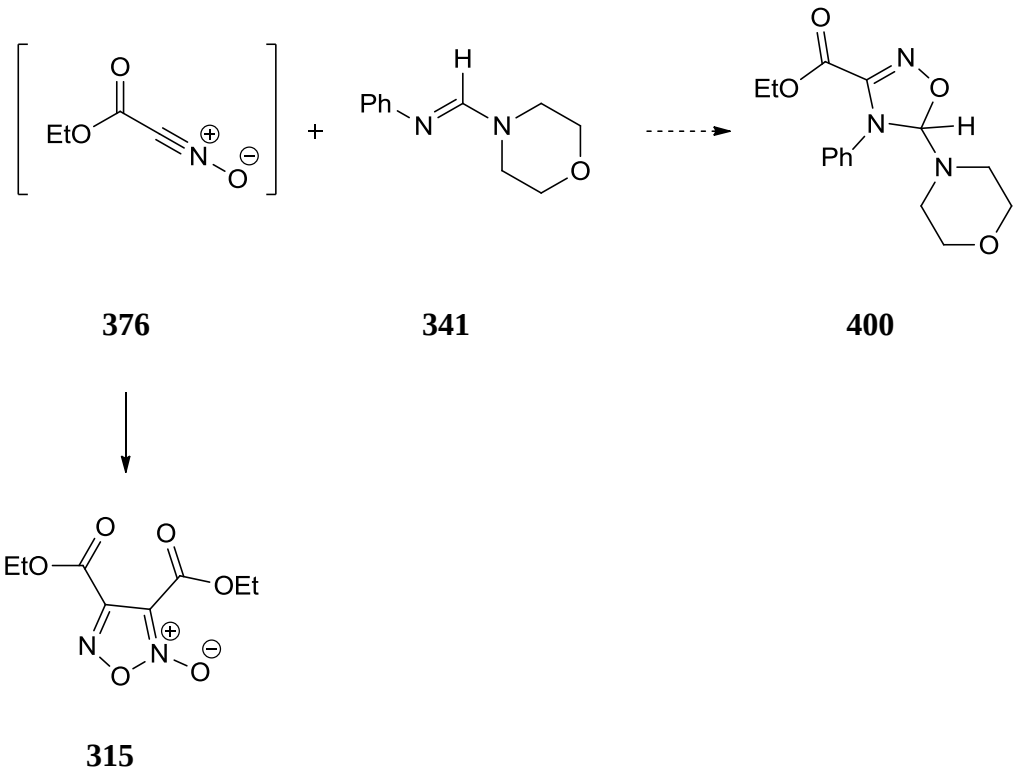
Combining this solution with the amidine produced a mixture of furoxan **431** and amidine **341** (1 : 1) (Scheme 258). Dimerisation of the nitrile oxide to furoxan **431** appears to be favoured over cycloaddition.



431

Scheme 258: The reaction of nitrile oxide 430 with amidine 341

The ^{1}H NMR spectroscopic data showed that nitrile oxide **376** had dimerised prior to the addition of amidine **341** in the synthesis of oxadiazoline **400** (Scheme 259). Subsequent NMR spectra showed that the dimer **315** and amidine **341** were present in equal quantities.

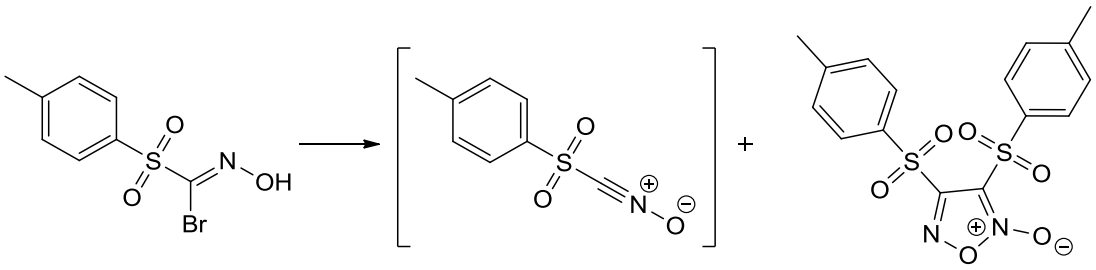


376 **341** **400**

315

Scheme 259: The attempted synthesis of oxadiazoline 400

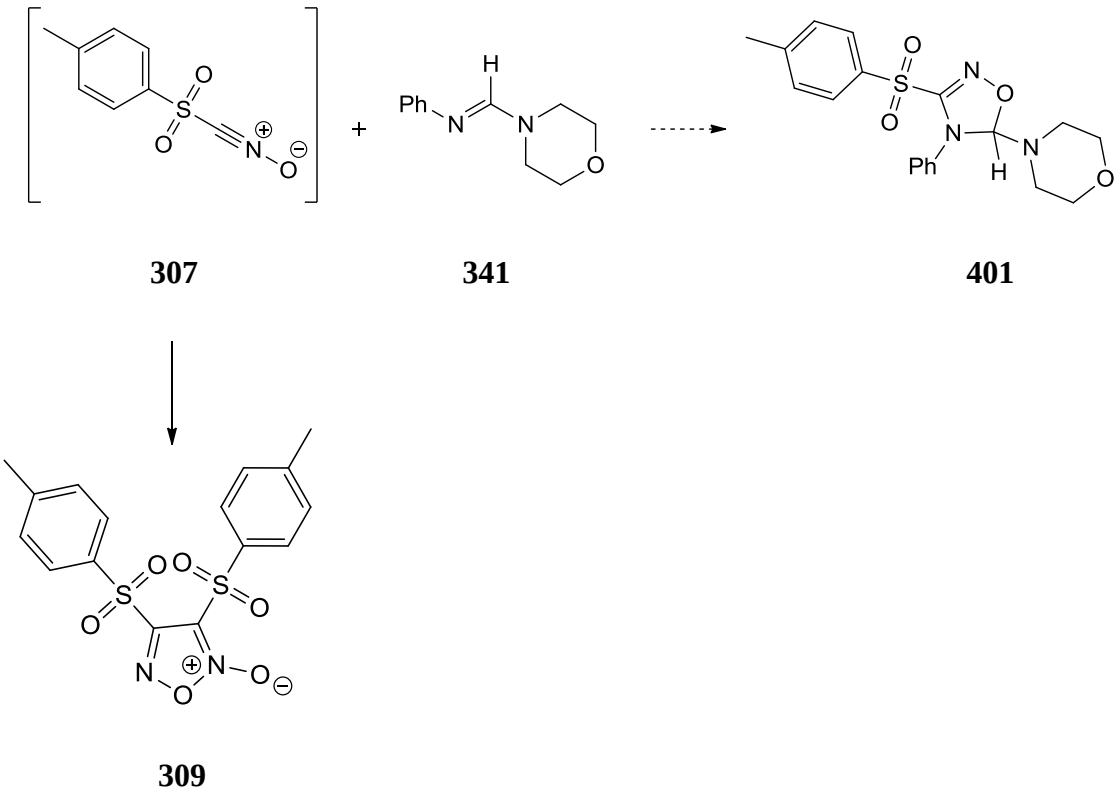
The combination of 1-(*p*-toluenesulfonyl)-1-bromoformaldoxime **299** with triethylamine gave a mixture of the nitrile oxide **307** and furoxan **309** (Scheme 260). (The ratio could not be established).



299 **307** **309**

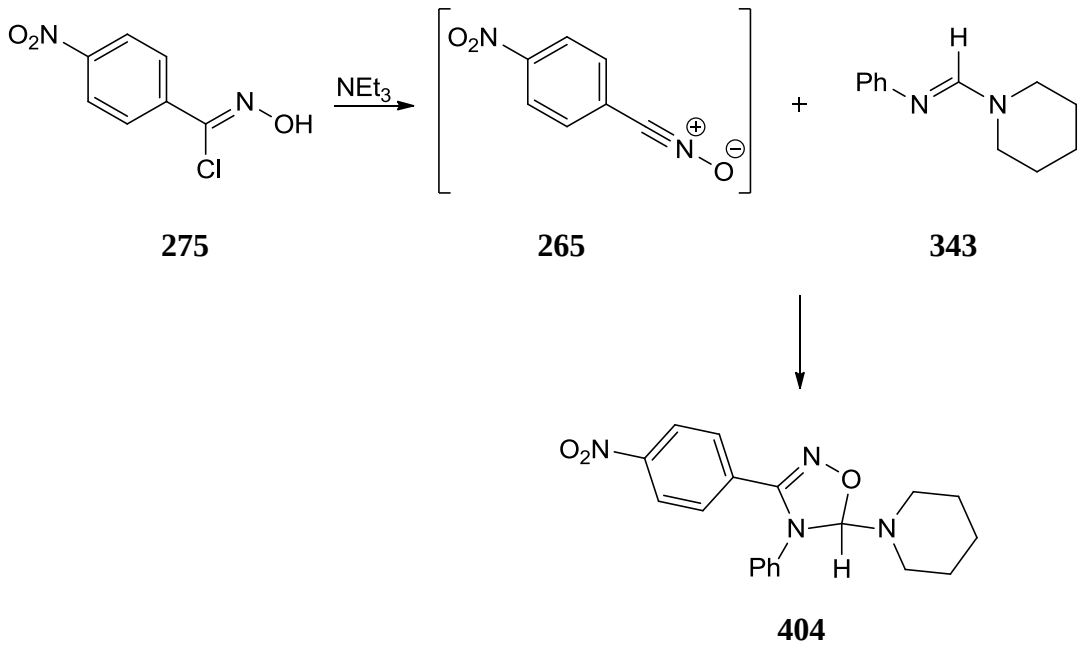
Scheme 260: The dehydrohalogenation of 299

When this solution was combined with amidine **341**, ^{1}H NMR spectroscopic analysis demonstrated that the furoxan **309** and amidine **341** were present in a ratio of 29 : 71 (Scheme 261). This indicates that nitrile oxide **307** favours dimerisation over cycloaddition and is too reactive to be pregenerated *in situ* prior to the addition of the dipolarophile.



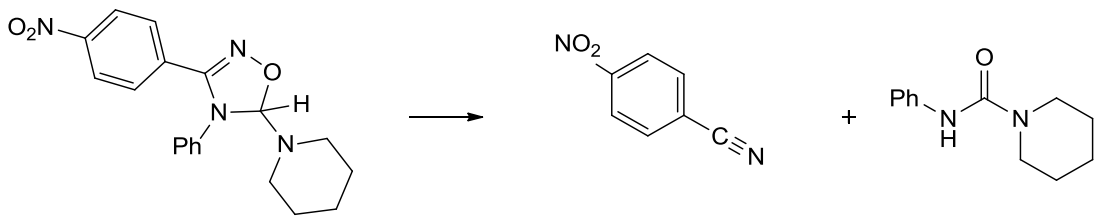
Scheme 261: The attempted synthesis of oxadiazoline 401

When the nitrile oxide **265** had been generated from *p*-nitrobenzohydroximoyl chloride **275** and combined with the amidine **343**, the oxadiazoline **404** was formed quantitatively (Scheme 262).



Scheme 262: The combination of nitrile oxide 265 with amidine 343 in the preparation of oxadiazoline 404

Subsequent proton NMR spectroscopic analysis (Figure 106) illustrated that conversion of oxadiazoline **404** to the nitrile **378** and urea **337** had occurred within 20.4 h after mixing the 1,3-dipole and dipolarophile (Scheme 263).



404 **378** **337**

Scheme 263: The conversion of the oxadiazoline 404 to the nitrile 378 and urea 337

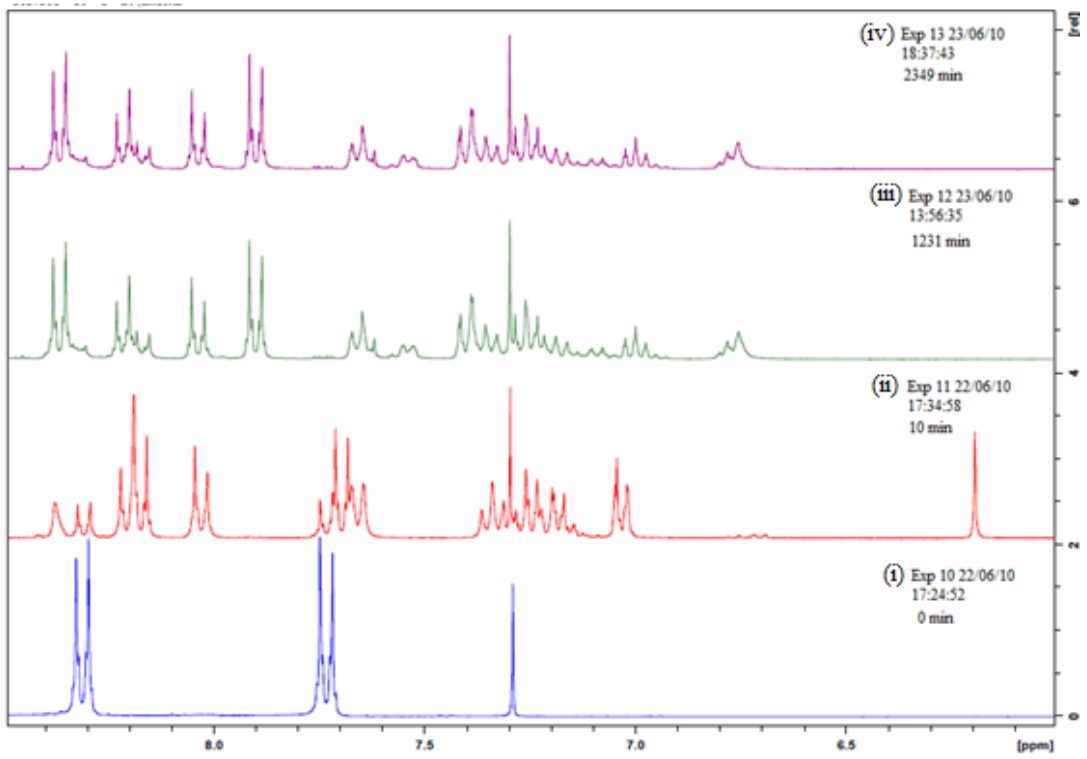
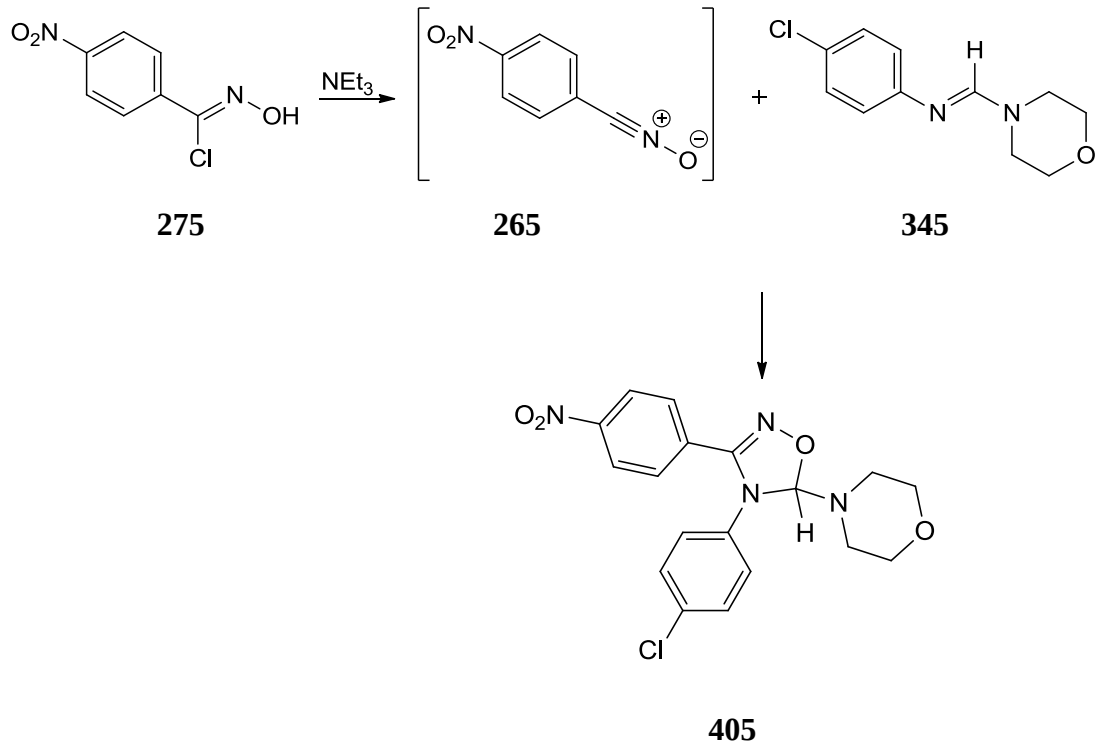


Figure 106: The NMR spectroscopic analysis of the reaction of *p*-nitrobenzohydroximoyl chloride 275 with amidine 343 in the presence of triethylamine as the base in $CDCl_3$ at 300K

The NMR spectroscopy tube dehydrohalogenation reaction of *p*-nitrobenzohydroximoyl chloride **275** with triethylamine and subsequent reaction with amidine **345** in the attempted preparation of oxadiazoline **405** was examined (Scheme 264). After addition of the nitrile oxide **265** solution to the amidine **345**, the oxadiazoline **405**, amidine **345** and nitrile oxide **265** were present (9 min after the addition of the dipolarophile) in a ratio of 58 : 24 : 18.

Within 1.1 h of mixing the reagents, the nitrile oxide **265** was completely consumed and the oxadiazoline **405** was formed.



275 **265** **345**

405

Scheme 264: The synthesis of oxadiazoline 405

The relative rate constant of the reaction was evaluated by plotting 1/[amidine] (M^{-1}) *versus* time (sec) and was found to be approximately 4.2 x 10^{-3} $M^{-1}s^{-1}$ at 300K (Figure 107). Thus, while the reaction of amidine **345** is still rapid, the presence of a moderately electron withdrawing substituent (Cl), is sufficient to slow the rate of reaction to a level where the oxadiazoline can be observed within a shorter period.

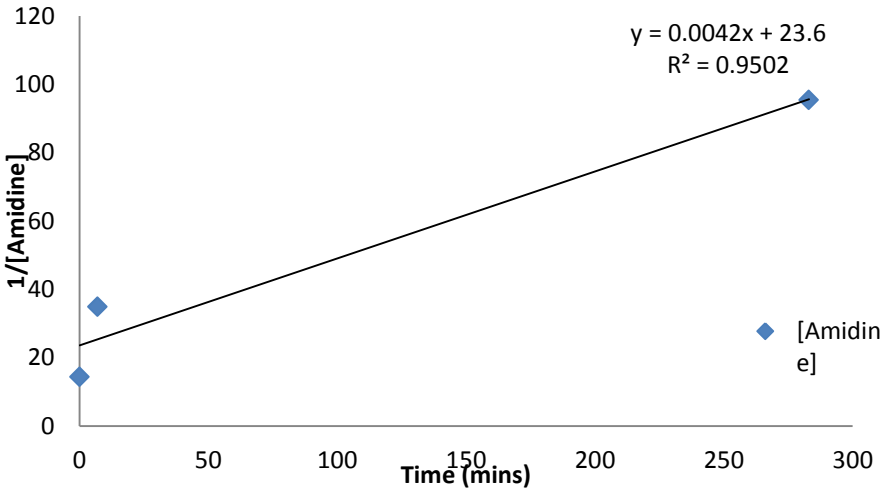
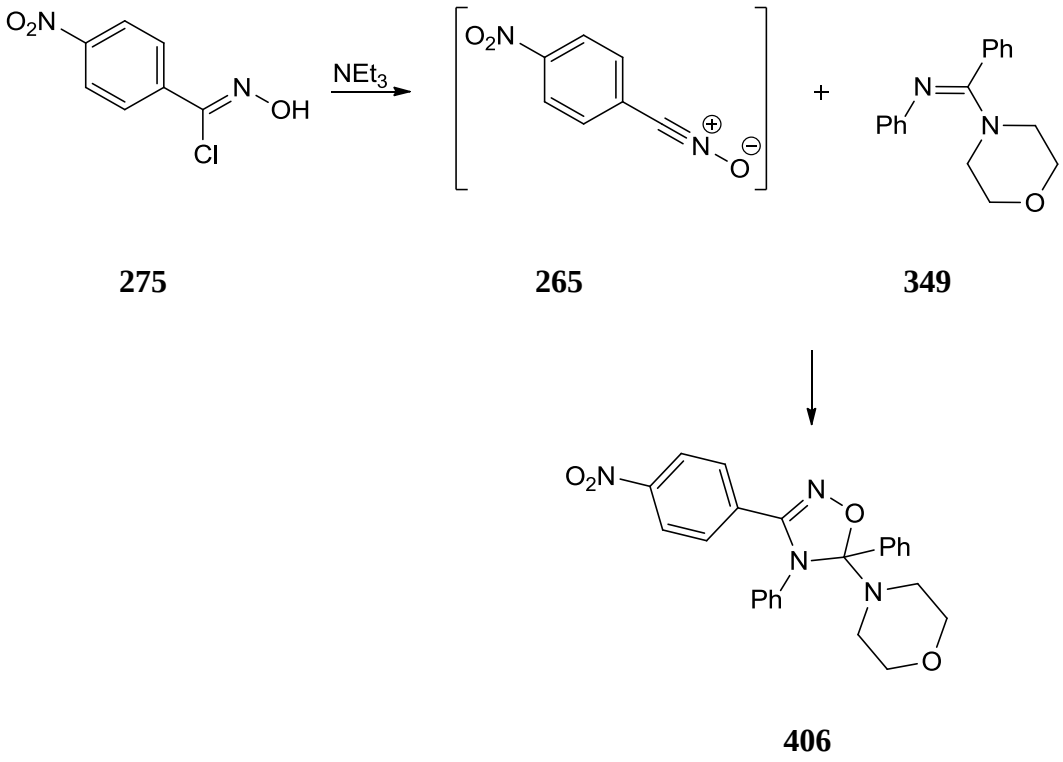


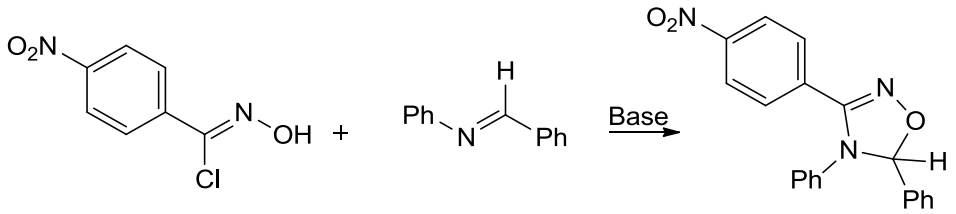
Figure 107: The determination of the second order relative rate constant, *k*, for the reaction of amidine 345 and nitrile oxide 265 by plotting 1/[amidine 345] against time (mins)

The initial step in the NMR spectroscopy tube reaction in the formation of oxadiazoline **406** involved the conversion of *p*-nitrobenzohydroximoyl chloride **275** to the nitrile oxide **265** (Scheme 265). Figure 106-i showed 100% conversion to nitrile oxide **265**. Addition of the resulting solution to amidine **349** (Figure 106-ii) showed that all of the nitrile oxide was consumed within 9 min in the formation of oxadiazoline **406**.



Scheme 265: The preparation of oxadiazoline 406

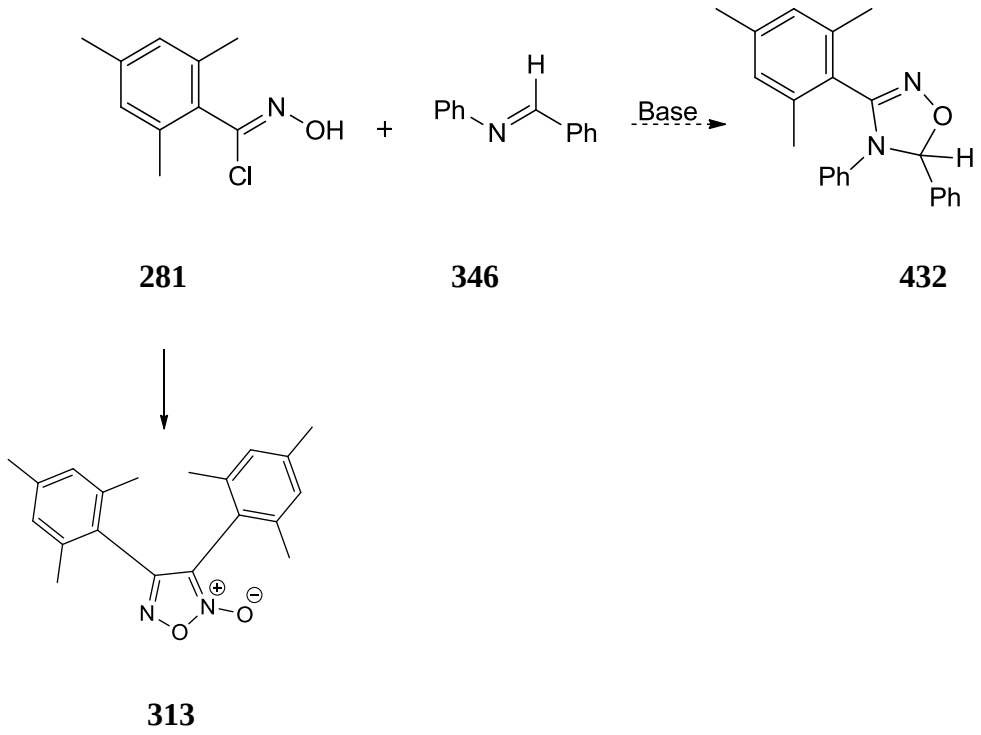
The presence of a small amount (<20%) of amidine **349** is probably due to stoichiometric differences (there is 0.07 μmol more of amidine than nitrile oxide). The result of this experiment demonstrated that the 1,3-dipolar cycloaddition took place within 9 min of mixing the reagents. This is still a fast rate of reaction given that the dipolarophile was a benzamidine, i.e. the additional phenyl group would be expected to exert a steric effect on the reaction rate. The reaction of *p*-nitrobenzohydroximoyl chloride **275** with imine **346** in the presence of triethylamine was also carried out as an NMR spectroscopy tube reaction (Scheme 266). The result of which, is that the full conversion to the oxadiazoline **420** was observed within 27 h.



275 **346** **420**

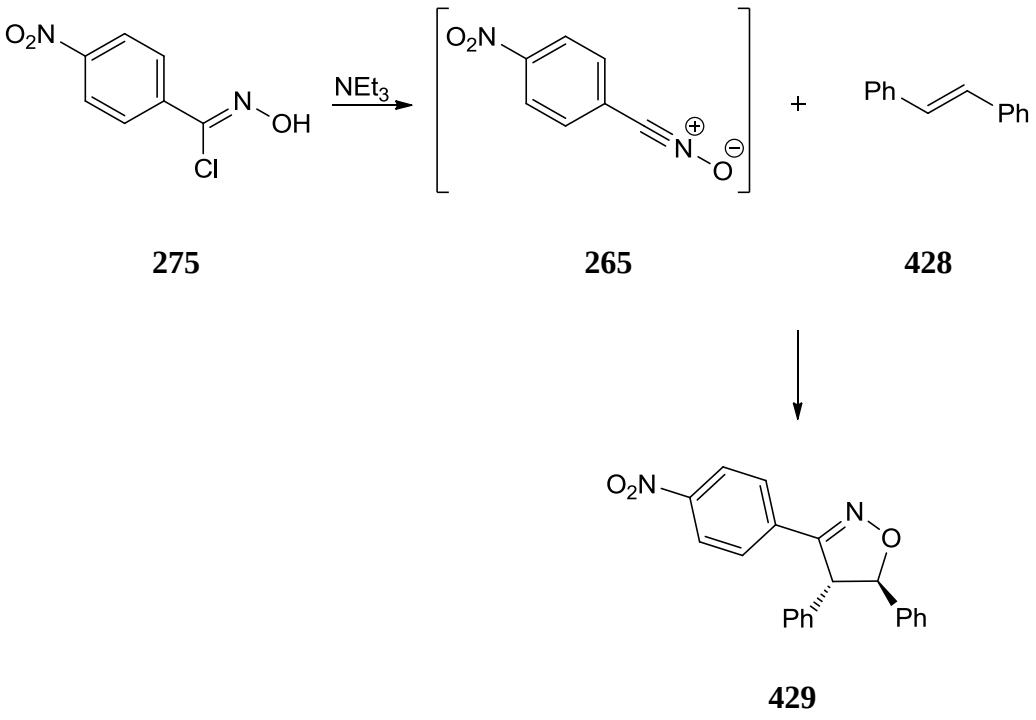
Scheme 266: The reaction of *p*-nitrobenzohydroximoyl chloride 275 with imine 346 in the presence of triethylamine

Following on from that cycloaddition, mesitonitrile-*N*-oxide **7** was reacted with imine **346** in a similar manner (Scheme 267). After 16.25 days, the imine **346** and furoxan **313** were present, indicating that the oxadiazoline **432** did not form under these conditions in this time frame.



Scheme 267: The reaction of 2,4,6-trimethylbenzohydroximoyl 281 with imine 346 in the attempted synthesis of oxadiazoline 432

The first spectra of the NMR spectroscopy tube reaction of *p*-nitrobenzohydroximoyl chloride **275** and triethylamine showed 100% conversion of hydroximoyl chloride **275** to the nitrile oxide **265**. Following the addition of the alkene **428**, ^{1}H NMR spectroscopic analysis was immediately carried out (Scheme 268).

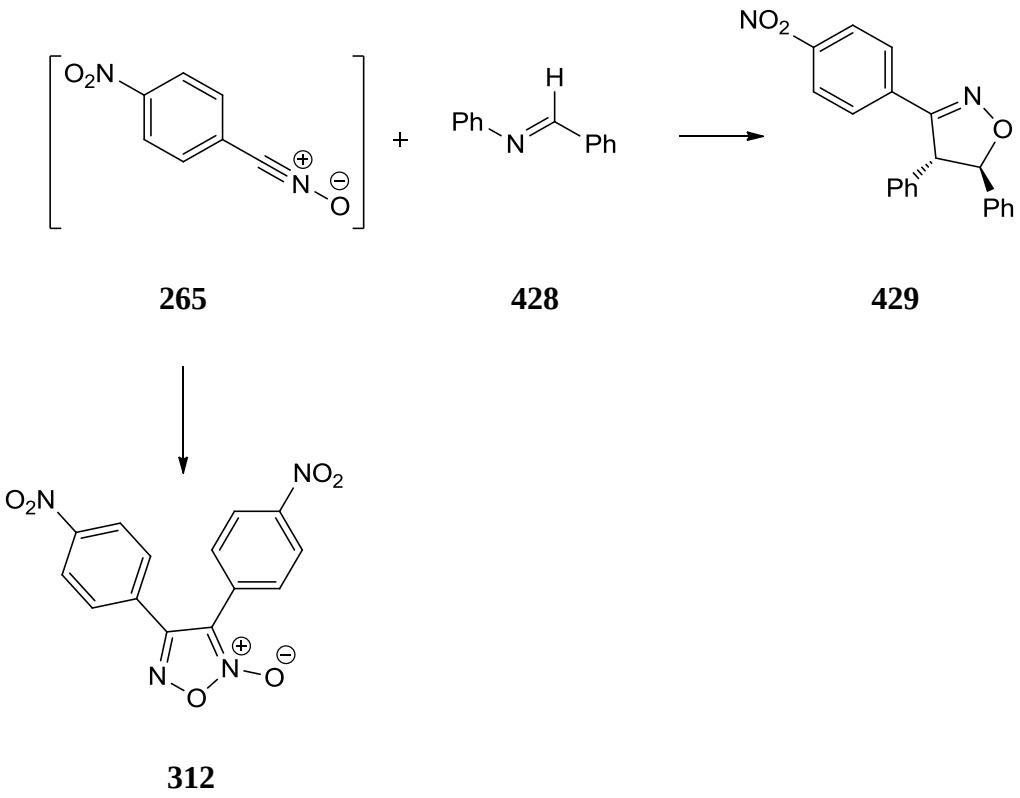


275 **265** **428**

429

Scheme 268: The reaction of hydroximoyl chloride 275 with alkene 428

This demonstrated that the 1,3-dipolar cycloaddition had not commenced immediately as both nitrile oxide **265** and alkene **428** were present. Twenty minutes after the combination of the nitrile oxide and the alkene, the isoxazoline **429** began to form. Subsequent spectra indicated that cycloaddition was continuing and the proportion of nitrile oxide **265** and alkene **428** were less. However, there is also evidence of the furoxan **312** forming at this point.



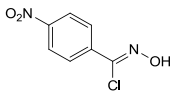
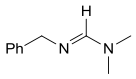
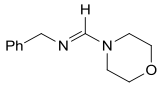
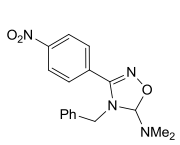
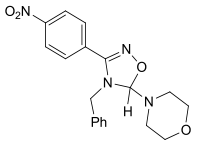
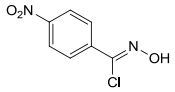
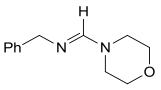
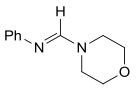
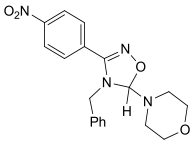
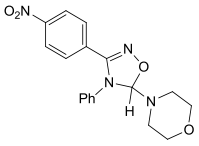
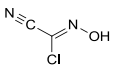
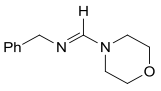
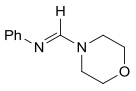
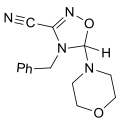
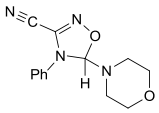
Scheme 269: The conversion of 265 with 428

The NMR spectroscopic analysis indicated that the majority of the isoxazoline **429** was formed within 4 h. Monitoring of the reaction continued for a total of 79 h, however the proportion of isoxazoline **429** formed did not further increase during this time. The formation of the furoxan **312** proved to be a competing reaction preventing complete conversion of the alkene **428** to the isoxazoline **429**.

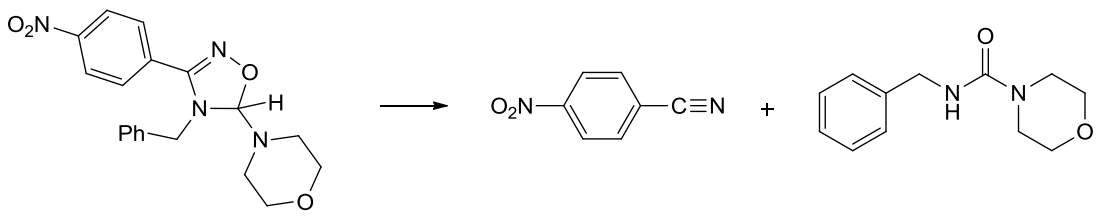
5 Competition reactions

We investigated selectivity of the formamidines for nitrile oxides by means of competition reactions in which a solution of the hydroximoyl halide was added to a solution of dipolarophiles and base. To investigate which dipolarophile was more reactive towards the nitrile oxide, the hydroximoyl halide solution was added to a mixture of the two formamidines to be screened. The ratio of oxadiazolines formed was measured using proton NMR spectroscopic analysis (Table 42).

Table 42: The products targetted in the reaction of hydroximoyl halide precursors with a mixture of two formamidines

Entry	Hydroximoyl Halide	Dipolarophiles		Products targetted
1	 **275**	 **339**	 **318**	 **367**  **381** (50 : 50)
2	 **275**	 **318**	 **341**	 **381**  **392** (84 : 16)
3	 **304**	 **318**	 **341**	 **390**  **402** (68 : 32)

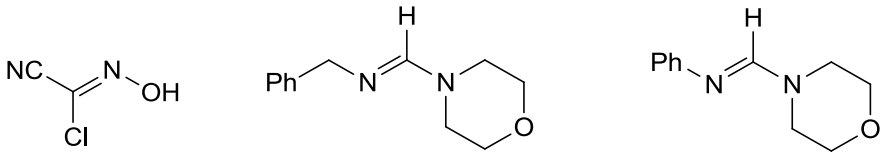
The product ratio was determined using the characteristic oxadiazoline H-5 proton resonances for each product. The shifts used are specified in the Experimental section, with detail for each competition experiment. Entry 1 in Table 42 shows that *p*-nitrobenzonitrile oxide did not have a preference for either of the formamidines assessed even though an *N*,*N*-dimethyl amino group is more electron donating than than a 4-morpholino substituent; the relative rate of reaction from the product ratio is (k_{rel}) = 1. Entry 2 (Table 42) demonstrates that oxadiazoline **392** was successfully produced using this procedure however the oxadiazoline **381** had undergone conversion to the corresponding nitrile **378** and urea **336** (Scheme 270).



381 **378** **336**

Scheme 270: The cycloreversion of oxadiazoline 381 to nitrile 378 and urea 336

Cyanoformhydroximoyl chloride **304** showed a 2:1 preference for the *N*-benzyl **318** rather than the *N*-phenyl formimidoyl **341** morpholine (Entry 3, Table 42).We attribute this difference to a combination of a reduced steric effect upon changing from *N*-phenyl to *N*-benzyl, coupled with an increased conjugation of the imine group in amidine **341** with the *N*-phenyl substituent.

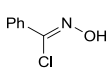
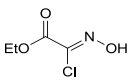
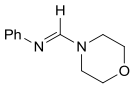
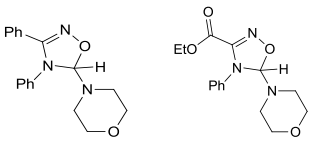
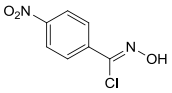
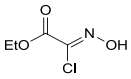
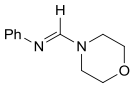
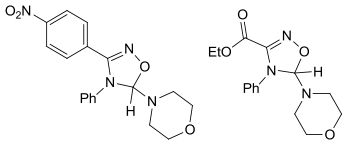
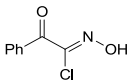
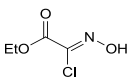
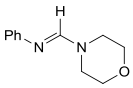
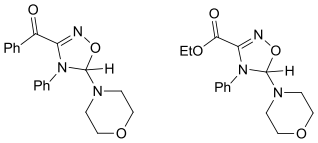


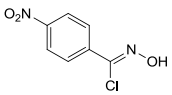
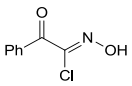
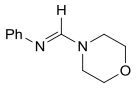
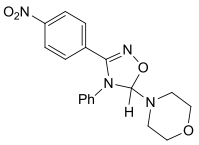
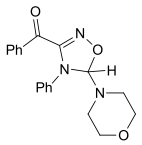
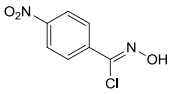
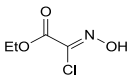
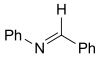
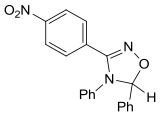
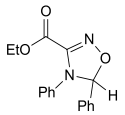
304 **318** **341**

Figure 108: The structures of 304, 318 and 341

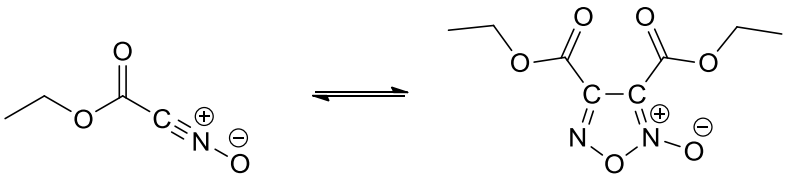
In order to identify the amidine for which the nitrile oxide had a preference, the procedure of adding equimolar amounts of the two hydroximoyl halides to the dipolarophile being assessed was adopted. The results of these competition experiments are summarised in Table 43.

Table 43: The products targetted in the reaction of formamidines with a mixture of two hydroximoyl halide precursors

Entry	Hydroximoyl Halide		Dipolarophiles	Products targetted
1	 **26**	 **295**	 **341**	 **267** **400** (59 : 41)
2	 **275**	 **295**	 **341**	 **392** **400** (63 : 37)
3	 **286**	 **295**	 **341**	 **398** **400** (60 : 40)

Entry	Hydroximoyl Halide		Dipolarophiles	Products targetted
4	 **275**	 **286**	 **341**	  **392** **398** (54 : 46)
5	 **275**	 **295**	 **346**	  **420** **426** (89 : 11)

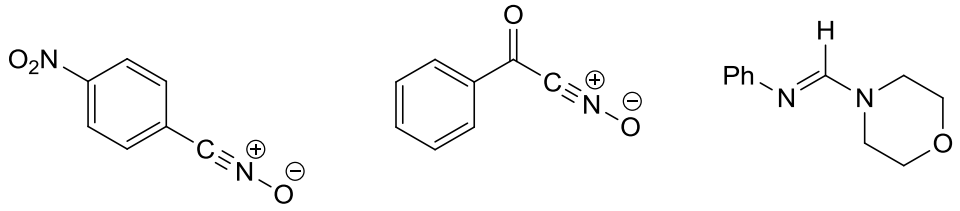
This method of assessment gave similar results across the board, as illustrated by the oxadiazoline ratios in Table 43. While it appears that the ethoxycarbonylnitrile-*N*-oxide **376** is less reactive than the other nitrile oxides presented in Table 43, a more realistic conclusion is that this nitrile oxide dimerised to furoxan **315** in competition with the amidine (Scheme 271). Therefore, the product ratios for Entries 1-3 suggest that the ethoxycarbonylnitrile-*N*-oxide **376** is marginally less reactive that the other nitrile oxide competitors. This conclusion could be invalid if the rate of dimerisation of the former nitrile oxide exceeds that for the cycloaddition process. If an allowance is made for this possibility, then it is reasonable to conclude that there is no difference in selectivity for reaction of amidine **341** with the nitrile oxides studied.



376 **315**

Scheme 271: The dimerisation of nitrile oxide 376 to furoxan 315

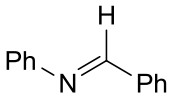
Likewise, the results (Entry 4) suggest little difference between *p*-nitrobenzonitrile oxide **265** and benzoylformonitrile-*N*-oxide **10** for amidine **341** even though the former 1,3-dipole is more stable (isolable) (Figure 109).



265 **10** **341**

Figure 109: The structures of 265, 10 and 341

Substitution of the 4-morpholine group with a phenyl ring (amidine **341** vs imine **346**) produces a more significant result in the cycloaddition selectivity experiment – compare Entries 2 and 5. It is clear that in this case, *p*-nitrobenzonitrile oxide **265** exhibits a significant preference for imine **346**. The competing dimerisation of ethoxycarbonylnitrile-*N*-oxide **376** would not be entirely sufficient to explain the product ratio observed. A favourable secondary interaction in the transition state for cycloaddition of the imine with *p*-nitrobenzonitrile oxide **265** could originate from a π-stacking interaction between the *N*-phenyl group of **346** and the *p*-nitrophenyl ring of the 1,3-dipole **265** (Figure 110).



346

Figure 110: Imine 346

6 Conclusions

The objective of our research was to investigate the synthesis & reactivity of nitrile oxides and their 1,3-dipolar cycloadditions of nitrile oxides with formamidines.

In our experience, methods described in the literature for generation of the nitrile oxide precursors are reliable on a small to medium scale. The preparation of the precursor of cyanoformonitrile oxide : CN(Cl)C=N-OH, is also reliable if conducted in accordance with the description of Tieman *et al.* but is either impractical or unreliable for the other published methods that we attempted.[164] We attributed the lack of success to a combination of poorly documented procedures for the precursor in one case, confusion about the use of chloral hydrate or anhydrous chloral in another and our view, an incorrect documentation of the procedure in the case of the Kozikowski route. We have no explanation for our lack of

success in the preparation of dichloroformaldoxime. Most of the yields and spectral analysis conform with those outlined in the literature. NMR spectroscopic analysis was a useful tool to monitor the generation of stable nitrile oxides. Carrying out the dehydrohalogenation reaction on an NMR spectroscopy scale enabled us to not only see the spectra of the 1,3-dipole immediately, but also to note its rates of reaction. In the case of *p*-nitrobenzonitrile oxide, the nitrile oxide was seen immediately upon addition of the base and the lifetime of the compound was *ca.* 15 h in chloroform-*d* at room temperature. This gave us valuable information on the likely reactivity of this nitrile oxide in 1,3-dipolar cycloaddition reactions and confirmed that generating the nitrile oxide *in situ* is the best option. Triethylamine was the best choice of base for a prompt dehydrohalogenation reaction.

The choice of base for the liberation of the nitrile oxide from the hydroximoyl halide precursor was important for other systems however. Experiments involving 1-*p*-toluenesulfonyl-1-bromoformaldoxime showed that bulkier bases such as DBU or milder bases such as potassium bicarbonate were not suitable to generate the nitrile oxide quantitatively from the hydroximoyl halide. In principal, one could influence the rate of cycloaddition of this nitrile oxide by selecting potassium carbonate ahead of triethylamine. Experiments carried out under the same reaction conditions with the former yielded a mixture of the nitrile oxide and its dimer (furoxan), whereas triethylamine gave the latter exclusively. If the rate of cycloaddition reaction was anticipated to be slow i.e. a less reactive dipolarophile involved, then potassium carbonate instead of triethylamine could help to reduce the rate of the competing dimerisation reaction. However, the more typical reaction procedure would be involve control of the addition of the hydroximoyl halide solution to a solution or a mixture of the base and dipolarophile.

The furoxan of *p*-nitrobenzonitrile-*N*-oxide was the quickest to form (complete within 15 h), with the dimer of mesitonitrile-*N*-oxide, being the slowest (complete within 15 days). Mid-way in the range was dibromofuroxan, which was observed in a solution of bromonitrile-*N*-oxide in chloroform-*d* by ^{13}C NMR spectroscopic analysis after 7 days.

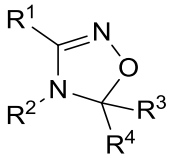
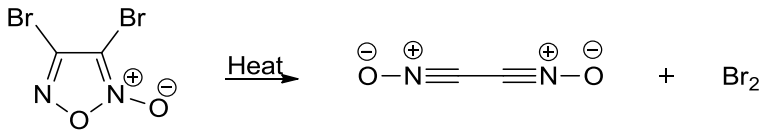


Figure 111: Δ^2-1,2,4-Oxadiazoline

Quite a number of nitrile oxides were generated in the course of this research. This facilitated a comparison of various substituents at the C-3 position of the oxadiazoline (Figure 111). A *p*-nitrophenyl- substituent at this position consistently yielded the corresponding oxadiazoline, regardless of the dipolarophile used. Mesitonitrile-*N*-oxide **7** gave the poorest cycloaddition result as it tended not to undergo the 1,3-dipolar cycloaddition reaction with the dipolarophiles explored. The propensity of ethoxycarboxynitrile oxide to self-dimerisation proved to be an ever-present competing reaction. The only cycloaddition of that dipole that did not yield a furoxan by-product was the reaction involving *N*-phenylformimidoylmorpholine as the dipolarophile.

The 1,3-dipolar cycloaddition reaction with dibromoformaldoxime as the nitrile oxide precursor was carried out with a number of dipolarophiles. All attempts failed to isolate the Δ^2-1,2,4-oxadiazoline from that compound. The anticipated decomposition products were a nitrile and a urea. However, an amide was isolated leading to the belief that a different mechanistic pathway was in operation for the 3-bromo compounds. Infrared spectra of the reaction mixtures isolated invariably showed a peak at ~2216 cm^{-1} which we believed indicated the presence of a nitrile or a heterocumulene. The IR absorption that we observed for the reaction product mixture is consistent with the presence of phenylcyanamide- comparison with spectra of an authentic sample of the compound, synthesised independently. A literature search for compounds with a similar intense peak at ~2220 cm^{-1}, revealed that dibromofuroxan **15** is a furoxan which does not liberate the bromonitrile oxide upon heating. Westwood *et al.* established that bromine gas was liberated and cyanogen *bis*-*N*-oxide **72** was formed (Scheme 272). They observed an IR absorption of 2227 and 1259 cm^{-1} which correlated to '*one molecular species*'.[12o]

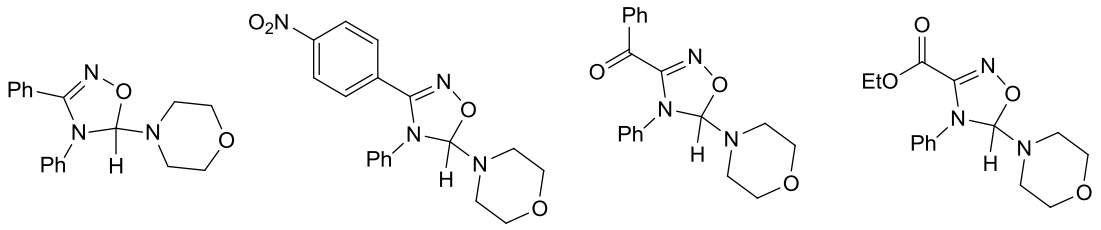


15 **72**

Scheme 272: The conversion of furoxan15 to yield cyanogen-*bis*-*N*-oxide 72

The potential stabilising effect of the subsituent at the C-3 position of the oxadiazoline is evident by comparing the degradation data of oxadiazolines **267** (R^1 = Ph, Figure 72), **392** (R^1 = *p*-NO_2Ph, Figure 78), **398** (R^1 = PhC(O), Figure 86) and **400** (R^1 = EtO_2C-, Figure 92) (Figure 112). Oxadiazoline **400** was the slowest to initiate degradation to *N*-

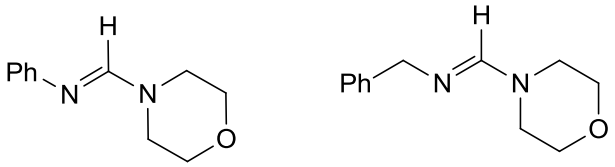
phenylmorpholine-4-carboxamide and ethoxycarbonylformonitrile taking ten days to reach a steady state of conversion. After 136 days, ~50% of the oxadiazoline still remained.



267 **392** **398** **400**

Figure 112: The structures of oxadiazolines 267, 392, 398 and 400

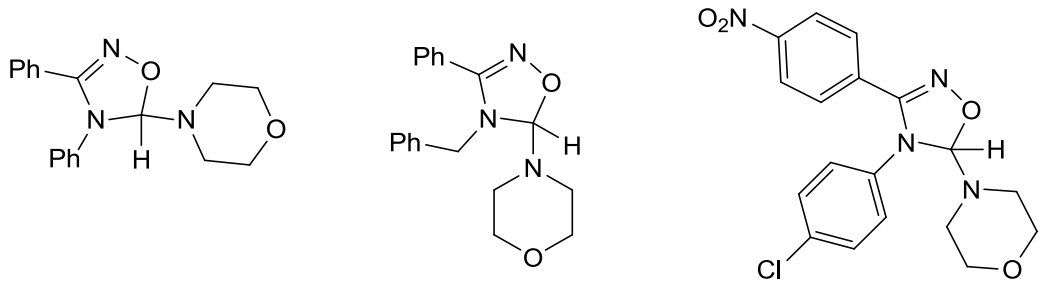
The data yielded from the cycloaddition reactions with amidines **341** and **318** as the dipolarophiles allowed a direct comparison the effect of a phenyl or benzyl substituent at R^2 of the oxadiazoline (Figure 113).



341 **318**

Figure 113: The amidines 341 and 318

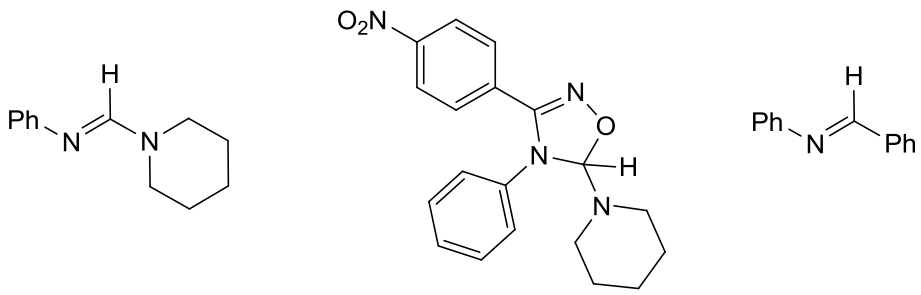
The benzyl group at R^2 tended to yield more reactive oxadiazolines that were difficult to isolate. The similarity in reactivity of a phenyl, benzyl or *p*-chlorophenyl substituent at the 4-position of the heterocycle was also examined. NMR spectroscopy tube experiments facilitated this and established that each of the oxadiazolines **267**, **380** and **405** were formed quantitatively on mixing of the reagents (Figure 114).



267 **380** **405**

Figure 114: The oxadiazolines 267, 380 and 405

Introduction of a more electron releasing *N*,*N*-dimethyl amino subsituent on C_5 of the oxadiazoline affected our ability to isolate the corresponding oxadiazolines (Figure 111). With a morpholine group at C-5 position, isolation of the oxadiazoline was dependent on the substituent R^2. In the case of cycloadditions with amidine **343**, short reaction times of up to ten minutes allowed for exclusive isolation of oxadiazoline in the case of oxadiazoline **404** (Figure 115). Reaction times extending beyond ten minutes yielded a mixture of oxadiazoline, nitrile and urea.



343 **404** **346**

Figure 115: The compounds 343, 404 and 346

When a comparison is made with the imine **346** as the dipolarophile, the reaction times are much slower. Therefore, an additional nitrogen substituent does impact the cycloaddition reaction rate and subsequent conversion of the oxadiazoline into nitrile plus urea. This outcome clearly demonstrates that the nature of the *N*-substituent (electron donating to moderately electron withdrawing) in the imine group of the amidine has little influence on the reactivity of the amidines towards *p*-nitrobenzonitrile oxide (see also the competition reaction data in Table 42 and Entry 4 in Table 43: the latter for comparison of reactivity of two nitrile oxides possessing electron withdrawing groups in their molecular structures). This conclusion does not however provide any evidence for a diffusion controlled rate of cycloaddition since an order or reactivity beyond what is measurable through preparative, millimole scale reactions over a short timescale. Further work on this issue would require use of a kinetics technique in the realm of stopped-flow methodology using either UV-visible or NMR spectroscopy as the analytical technique.

Chapter 3
Experimental

1 General procedures

Solvents were distilled prior to use: hexane and ethyl acetate were distilled from phosphorous pentoxide. Dichloromethane was also distilled from phosphorous pentoxide, and when needed in an anhydrous state, it was redistilled from calcium hydride and stored over activated 4Å molecular sieves. THF was distilled from sodium in the presence of benzophenone. Pyridine was distilled from sodium hydroxide and was subsequently distilled from calcium hydride. Triethylamine was distilled from calcium hydride. DMSO was distilled from calcium hydride under reduced pressure and stored over activated 4Å molecular sieves. Dry solvents were obtained by standard procedure.[207] Infrared (IR) spectra were recorded on a Perkin-Elmer Paragon 1000 and Perkin Elmer Spectrum One. Liquid samples were examined as thin films interspersed between sodium chloride plates. IR spectra of solids were measured as KBr discs.

^{1}H NMR spectra were recorded on a Bruker AVANCE 300, Bruker AVANCE 400, Bruker AVANCE 500 and Bruker AVANCE 600 spectrometers. ^{13}C NMR spectra were recorded on a Bruker AVANCE 300, 500 and 600 instruments at 75, 125 and 150MHz respectively. All spectra were recorded at 20°C in deuterated chloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard unless otherwise stated. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in Hertz (Hz). Splitting patterns in ^{1}H spectra are designated as s (singlet), bs (broad singlet), bd (broad doublet), bt (broad triplet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), ddt (doublet of doublet of triplets), ABq (AB quartet) and (m) multiplet.

Organic solutions were dried using anhydrous magnesium sulphate ($MgSO_4$). Thin layer chromatography (TLC) was performed on precoated silica gel (Merck HF_{254}) plates and compounds were visualised under ultraviolet light. Column "wet flash" chromatography was performed using **FLUKA** high-purity grade silica gel with a pore size of 60 Å, a 220-440 mesh particle size and 35-75 μm particle size (catalogue number **60738**). Bulb to bulb distillations were carried out on a Buchi GKR-50 Kugelröhr apparatus and the oven temperature is given as the boiling point of the substrate.

Chlorine gas was generated by the dropwise addition of conc. HCl to solid $KMnO_4$. HCl gas was removed by bubbling the gas through water. The chlorine gas was dried by bubbling through H_2SO_4.

HCl gas was generated by the dropwise addition of conc. H_2SO_4 on solid ammonium chloride and dried by its passage through conc. H_2SO_4 in a train of Dreschel bottles.

In cases where a synthesis proved successful, the same procedure was executed in the preparation of families of compounds, e.g. the method used in the preparation of 1-benzoyl-1-chloroformaldoxime was used in the preparation of 1-(*p*-bromobenzoyl)-1-chloroformaldoxime from the related starting material.

2 Appendix 1: Abbreviations

Δ: Heat

Ac: Acetyl

Bn: Benzyl

BnBr: Benzyl bromide

n-BuLi : *n*-Butyl lithium

*t*BuOCl: *t*-Butyl hypochlorite

Bu_3SnCl: Tri-*n*-butyltin chloride

$(Bu_3Sn)_2O$: *Bis*-Tributyltin oxide

$(Bu_4N)_2S_2O_8$: Tetrabutylammonium Peroxydisulphate

nBu_4NI: Tetra-*n*-butylammonium iodide

Cs_2CO_3: Caesium carbonate

$Cu(CHCO_2)_2.Ni(HCO_2)_2$:

DBU: 1,8-Diazabicyclo [5.4.0]-undec-7-ene

DCM: Dichloromethane

DIBALH: Di-*iso*butylaluminium hydride

DIC: *N*,*N*-Di*iso*propylcarbodiimide

DIEA: Di-*iso*propylethylamine

DMAP: 4-*N*,*N*-Dimethylaminopyridine

EtMgBr: Ethylmagnesium bromide

EWG: Electron-withdrawing group

Et_2Zn : Diethylzinc

FMO: Frontier molecular orbital

F/mol: Faraday/mole

HOMO: Highest occupied molecular orbital

HPLC: High performance liquid chromatography

LAH: Lithium aluminium hydride

LUMO: Lowest unoccupied molecular orbital

MEM: *β*-Methoxyethoxymethyl ether

$MeSO_2Cl$: Methanesulfonyl chloride

Mes: Mesityl group

MW: Microwave irradiation

$NaBrO_2$: Sodium bromite

$NaHCO_3$: Sodium bicarbonate

NBS: *N*-Bromosuccinimide

NCS: *N*-Chlorosuccinimide

$NH_2OH.HCl$: Hydroxylamine hydrochloride

NOE: nuclear Overhauser effect

Pd_2dba_3: *Tris*(dibenzylideneacetone)dipalladium (0)

$Pb(OAc)_4$: Lead tetraacetate

PCl_5: Phosphorous pentachloride

$PhI(OAc)_2$: Diacetoxyiodobenzene

PyBroP: Bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate

rt: Room temperature

$SOCl_2$: Thionyl chloride

TCBDA: *N*,*N*,*N'*,*N'*-Tetrachlorobenzene-1,3-disulfonamide

TCCA: Trichloroisocyanuric acid

TEOF: Triethyl *ortho*formate

TFAA: Trifluoroacetic anhydride

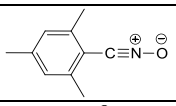
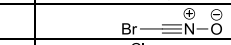
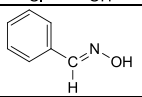
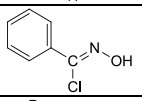
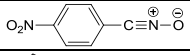
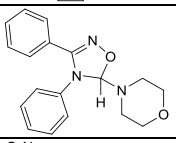
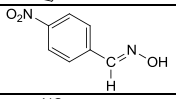
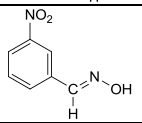
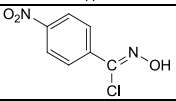
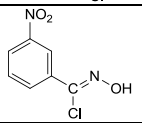
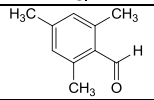
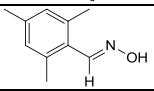
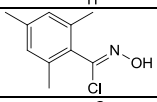
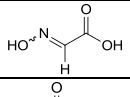
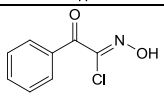
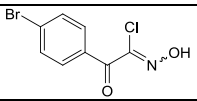
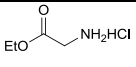
p-TSA: *p*-Toluenesulfonic acid

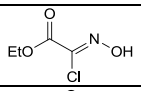
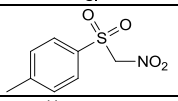
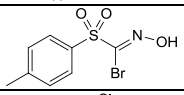
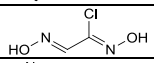
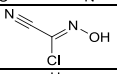
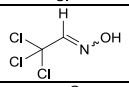
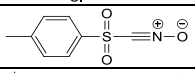
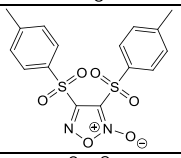
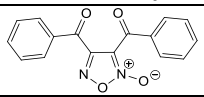
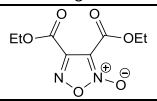
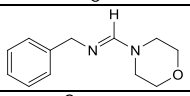
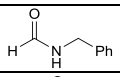
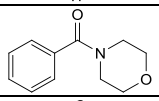
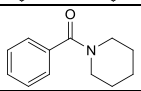
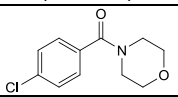
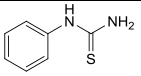
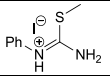
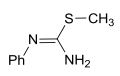
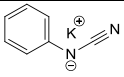
THF: Tetrahydrofuran

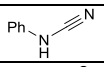
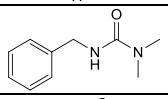
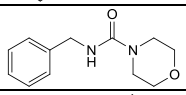
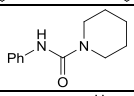
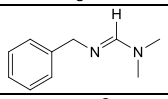
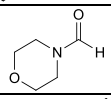
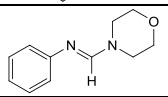
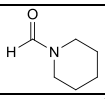
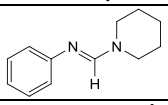
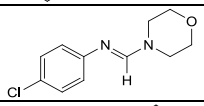
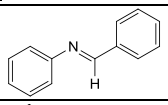
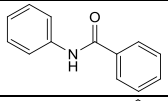
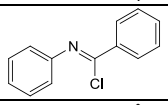
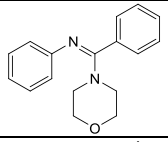
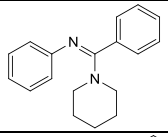
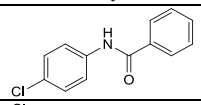
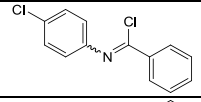
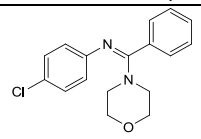
t.l.c.: Thin layer chromatography

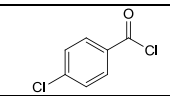
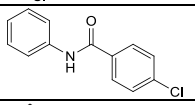
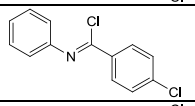
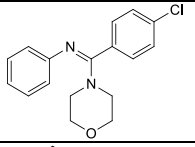
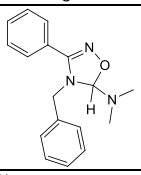
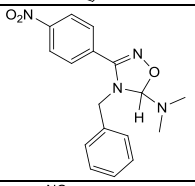
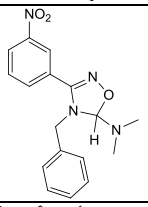
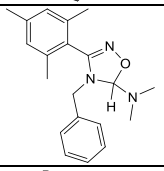
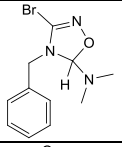
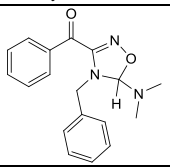
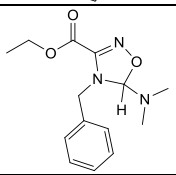
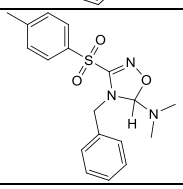
TMS: Trimethylsilyl

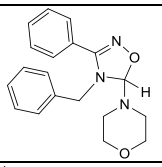
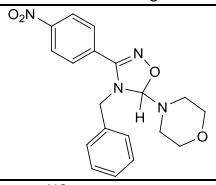
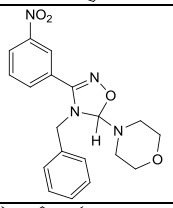
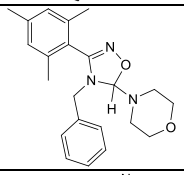
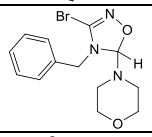
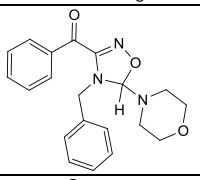
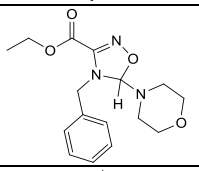
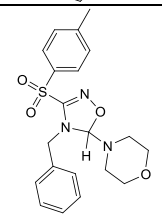
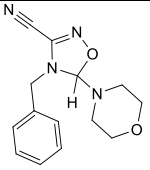
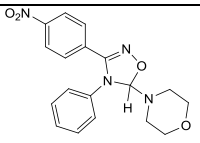
3 Appendix 2: Compound reference guide

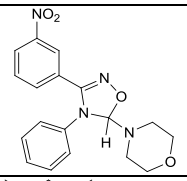
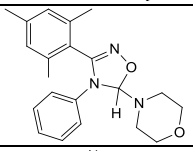
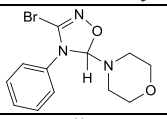
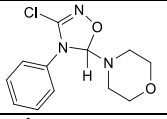
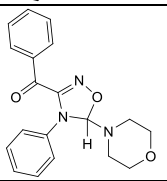
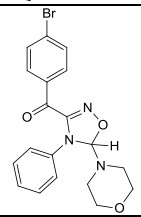
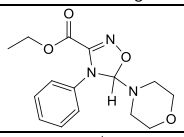
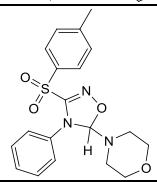
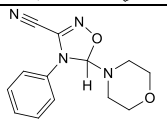
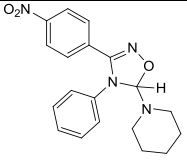
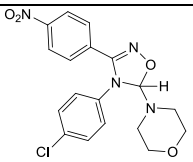
Compound number	Compound name	Compound structure	Section
7	Mesitonitrile-*N*-oxide		5.1.2
13	Bromoformonitrile-*N*-oxide		5.1.3
16	Dichloroformaldoxime		4.2.3
25	Benzaldoxime		4.1.1
26	Benzohydroximoyl chloride		4.1.2
41	Dibromoformaldoxime		4.2.1
265	*p*-Nitrobenzonitrile-*N*-oxide		5.1.1
267	3-Phenyl-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.1
272	*p*-Nitrobenzaldoxime		4.1.3
274	*m*-Nitrobenzaldoxime		4.1.5
275	*p*-Nitrobenzohydroximoyl chloride		4.1.4
276	*m*-Nitrobenzohydroximoyl chloride		4.1.6
279	Mesitaldehyde		4.1.7
280	Mesitaldoxime		4.1.8
281	2,4,6-Trimethylbenzohydroximoyl chloride		4.1.9
283	Glyoxylic acid aldoxime		4.2.2
286	1-Benzoyl-1-chloroformaldoxime		4.3.1
292	1-(*p*-Bromobenzoyl)-1-chloroformaldoxime		4.3.2
294	Glycine ethyl ester hydrochloride		4.4.1

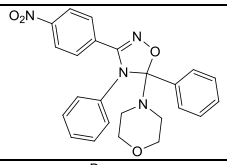
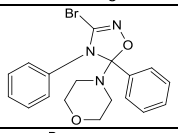
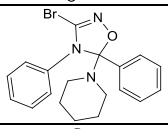
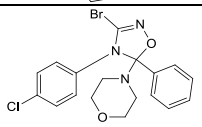
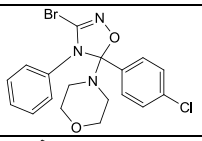
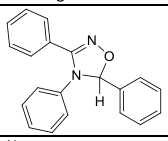
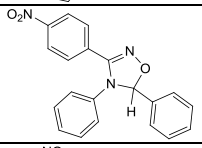
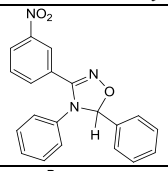
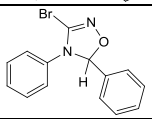
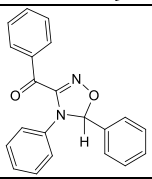
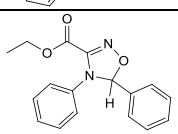
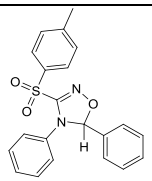
Compound number	Compound name	Compound structure	Section
295	Ethylchloroglyoxalate oxime		4.4.2
297	*p*-Toluenesulfonylnitromethane		4.4.3
298	Diazomethane		4.4.5
299	1-*p*-Toluenesulfonyl-1-bromoformaldoxime		4.4.4
303	Chloroglyoxime		4.4.6
304	Cyanoformohydroximoyl chloride		4.4.8
305	Chloral oxime		4.4.7
307	*p*-Toluenesulfonylformo-nitrile-*N*-oxide		5.1.4
309	3,4-*bis*-(*p*-Toluenesulfonyl)-furoxan		5.2.3
314	3,4-Dibenzoylfuroxan		5.2.1
315	3,4-Diethoxycarbonylfuroxan		5.2.2
318	*N*-Benzylformimidoylmorpholine		7.1.3
319	*N*-Benzylformamide		6.1.1
322	*N*-Benzoylmorpholine		6.2.1
324	*N*-Benzoylpiperidine		6.2.2
327	*N*-(*p*-Chlorobenzoyl)-morpholine		6.2.3
329	*N*-Phenylthiourea		6.2.4
330	Methyl-*N*-phenylcarbamidothioate hydroiodide		6.2.5
331	*N*-Phenyl-*S*-methylisothiourea		6.2.6
332	Potassium phenylcyanamide		6.2.7

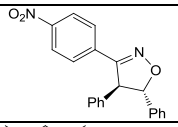
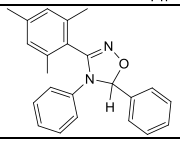
Compound number	Compound name	Compound structure	Section
333	Phenylcyanamide		6.2.8
335	1-Benzyl-3-(*N*,*N*-dimethyl)-urea		6.3.1.1
336	*N*-Benzylmorpholine-4-carboxamide		6.3.1.2
337	*N*-Phenyl-1-piperidine carboxamide		6.3.1.3
339	*N*,*N*-Dimethyl-*N´*-benzylformamidine		7.1.1
340	*N*-Formylmorpholine		7.1.2
341	*N*-Phenylformimidoylmorpholine		7.1.4
342	*N*-Formylpiperidine		7.1.5
343	*N*-Phenylformimidoylpiperidine		7.1.6
345	*N*-(*N´-p*-Chlorophenylformimidoyl)-morpholine		7.1.7
346	*N*-Benzylideneaniline		7.2.1
347	*N*-Benzoylaniline		7.3.1
348	*N*-Phenylbenzimidoyl chloride		7.3.2
349	*N*-(*N´*-Phenylbenzimidoyl)-morpholine		7.3.3
350	*N*-(*N´*-Phenylbenzimidoyl)-piperidine		7.3.4
351	*N*-Benzoyl-*p*-chloroaniline		7.3.5
352	*N*-*p*-Chlorophenylbenzimidoyl chloride		7.3.6
353	*N*-(*p*-Chlorophenyl)-benzimidoylmorpholine		7.3.7

Compound number	Compound name	Compound structure	Section
354	*p*-Chlorobenzoyl chloride		7.3.8
355	*N*-(*p*-Chlorobenzoyl)-aniline		7.3.9
356	*N*-Phenyl-(*p*-chlorobenzimidoyl) chloride		7.3.10
357	*N*-Phenyl-(*p*-chlorobenzimidoyl)-morpholine		7.3.11
366	3-Phenyl-4-benzyl-5-(*N´*,*N´*-dimethyl)-Δ^2,1,2,4-oxadiazoline		8.1.1.1
367	3-(*p*-Nitrophenyl)-4-benzyl-5-(*N´*,*N´*-dimethyl)-Δ^2,1,2,4-oxadiazoline		8.1.1.2
368	3-(*m*-Nitrophenyl)-4-benzyl-5-(*N´*,*N´*-dimethyl)-Δ^2,1,2,4-oxadiazoline		8.1.1.3
369	3-(2,4,6-Trimethylphenyl)-4-benzyl-5-(*N´*,*N´*-dimethyl)-Δ^2,1,2,4-oxadiazoline		8.1.1.4
370	3-Bromo-4-benzyl-5-(*N´*,*N´*-dimethyl)-Δ^2,1,2,4-oxadiazoline		8.1.1.5
373	3-Benzoyl-4-benzyl-5-(*N´*,*N´*-dimethyl)-Δ^2,1,2,4-oxadiazoline		8.1.1.6
374	3-Ethoxy-4-benzyl-5-(*N´*,*N´*-dimethyl)-Δ^2,1,2,4-oxadiazoline		8.1.1.7
375	3-(*p*-Toluenesulfonyl)-4-benzyl-5-(*N´*,*N´*-dimethyl)-Δ^2,1,2,4-oxadiazoline		8.1.1.8

Compound number	Compound name	Compound structure	Section
380	3-Phenyl-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.2.1
381	3-(*p*-Nitrophenyl)-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.2.2
382	3-(*m*-Nitrophenyl)-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.2.3
384	3-(2,4,6-Trimethylphenyl)-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.2.4
385	3-Bromo-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.2.5
386	3-Benzoyl-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.2.6
388	3-Ethoxy-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.2.7
389	3-(*p*-Toluenesulfonyl)-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.2.8
390	3-Cyano-4-benzyl-5-(4'-morpholine)-Δ^2-1,2,4-oxadiazoline		8.1.2.9
392	3-(*p*-Nitrophenyl)-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.2

Compound number	Compound name	Compound structure	Section
393	3-(*m*-Nitrophenyl)-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.3
394	3-(2,4,6-Trimethylphenyl)-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.4
396	3-Bromo-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.5
397	3-Chloro-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.6
398	3-Benzoyl-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.7
399	3-(*p*-Bromobenzoyl)-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.8
400	3-Ethoxy-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.9
401	3-(*p*-Toluenesulfonyl)-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.10
402	3-Cyano-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.3.11
404	3-(*p*-Nitrophenyl)-4-phenyl-5-piperidino-Δ^2-1,2,4-oxadiazoline		8.1.4.1
405	3-(*p*-Nitrophenyl)-4-(*p*-chlorophenyl)-5-(*N*-morpholino)-Δ^2-1,2,4-oxadiazoline		8.1.5.1

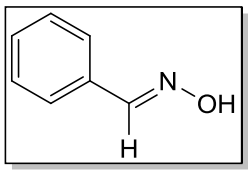
Compound number	Compound name	Compound structure	Section
406	3-(*p*-Nitrophenyl)-4-phenyl-5-phenyl-5'-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.2.1.1
407	3-Bromo-4,5-*di*phenyl-5'-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline		8.2.1.2
416	3-Bromo-4,5-*di*phenyl-5'-(*N*-piperidino)-Δ^2-1,2,4-oxadiazoline		8.2.2.1
417	3-Bromo-4-(*p*-chlorophenyl)-5-phenyl-5'-(*N*-morpholino)-Δ^2-1,2,4-oxadiazoline		8.2.3.1
418	3-Bromo-4-phenyl-5-(*p*-chlorophenyl)-5'-(*N*-morpholino)-Δ^2-1,2,4-oxadiazoline		8.2.4.1
419	Phenyl-4-phenyl-5-phenyl-Δ^2-1,2,4-oxadiazoline		8.3.1.1
420	3-(*p*-Nitrophenyl)-4-phenyl-5-phenyl-Δ^2-1,2,4-oxadiazoline		8.3.1.2
421	3-(*m*-Nitrophenyl)-4-phenyl-5-phenyl-Δ^2-1,2,4-oxadiazoline		8.3.1.3
424	3-Bromo-4-phenyl-5-phenyl-Δ^2-1,2,4-oxadiazoline		8.3.1.5
425	3-Benzoyl-4-phenyl-5-phenyl-Δ^2-1,2,4-oxadiazoline		8.3.1.6
426	3-Ethoxy-4-phenyl-5-phenyl-Δ^2-1,2,4-oxadiazoline		8.3.1.7
427	3-(*p*-Toluenesulfonyl)-4-phenyl-5-phenyl-Δ^2-1,2,4-oxadiazoline		8.3.1.8

Compound number	Compound name	Compound structure	Section
429	*Trans*-3-(*p*-nitrophenyl)-4,5-*di*phenyl-1,2-isoxazoline		8.3.2.1
432	3-(2,4,6-Trimethylphenyl)-4-phenyl-5-phenyl-Δ^2-1,2,4-oxadiazoline		8.3.1.4

4 Preparation of nitrile oxide precursors

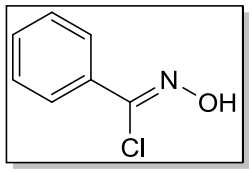
4.1 Synthesis of substituted benzohydroximoyl chlorides

4.1.1 Benzaldoxime[208] 25



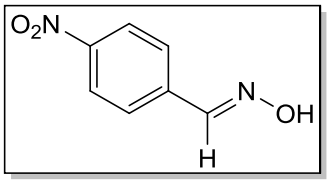
A solution of sodium hydroxide (44.1 g, 1.1 mol) in water (120 mL) was added dropwise *via* a pressure-equalising addition funnel to a stirring benzaldehyde (63.7 g, 0.6 mol). Addition took 2 hr 30 min, and a pale white gloopy solution resulted. Hydroxylamine hydrochloride (41.9 g, 0.6 mol) was added to the stirring solution. The pale yellow solution which resulted was stirred at room temperature for 1.5 h and sufficient water was added to reform the clear solution (~80 mL). The solution was stirred overnight. $CO_{2(g)}$ was bubbled through the stirring solution (for 135 min) until a thick oily emulsion formed. Water (500 mL) was added and the mixture was extracted with ether (200 mL first, then 2 x 80 mL). The combined organic extracts were dried and the solvent removed *in vacuo*. Sample was purified by distillation and the *oxime* (59.73 g, 82%) was isolated as clear oil, b.p. 114-124 ^{o}C @ 15 mmHg, (Lit. b.p. 122-124 ^{o}C @ 12 mmHg). ν_{max} (film): 3306, 1632, 1494, 1446, 1304, 1210 cm^{-1}; δ_H: 7.37 (3H, m, *m*- & *p*-ArH), 7.57 (2H, m, *o*-ArH), 8.17 (1H, s, CH=N), 9.32 (1H, bs, OH).

4.1.2 Benzohydroximoyl chloride[145b] 26



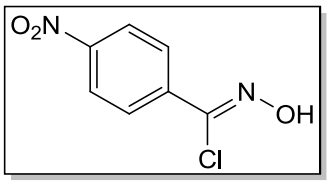
Chlorine gas was bubbled through a cooled (<0 ^{o}C, salt/ice water), stirring solution of benzaldoxime (12.16 g, 0.1 mol) in chloroform (150 mL) - a $CaCl_2$ guard tube was fitted to the reaction flask. The temperature was maintained at -10 ^{o}C and the chlorine gas caused the solution to go from clear through yellow, dark yellow/green, dark green, dark blue/green, blue, bright green, yellow/green, yellow, yellow/orange and finally to a dark orange indicating saturation with chlorine. The flask was stoppered, sealed and left in a freezer overnight. Excess chlorine was evaporated in a nitrogen stream (5 h). The solvent was removed *in vacuo* and the resulting dark red/orange residue was diluted with hexane (~20 mL) and placed in a freezer. The resultant solid was isolated by vacuum filtration to give the *hydroximoyl chloride* (6.73 g, 43%) as a pale cream solid, m.p. 51 ^{o}C (Lit. 48-50 ^{o}C). ν_{max} (KBr): 1628, 1491, 1238 cm^{-1}; δ_H: 7.42 (3H, m, *m*- & *p*-Ar-CH), 7.85 (2H, m, *o*-Ar-CH), 8.04 (1H, s, OH). δ_C: 127.6, 128.9 and 131.13 (3 x ArCH), 132.82 (*ipso* C of Ar), 140.5 (C=N).

4.1.3 *p*-Nitrobenzaldoxime[209] 272



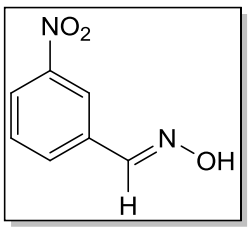
p-Nitrobenzaldehyde (37.95 g, 0.25 mol), hydroxylamine hydrochloride (17.47 g, 0.25 mol) and sodium acetate (41.01 g, 0.50 mol) were heated under reflux for 28 h in 95% ethanol (600 mL). The solvent was evaporated and the resulting yellow residue was dissolved in 2 M NaOH (600 mL) and the solution was stirred overnight. Water (1000 mL) was then added and a bright orange solution resulted. It was then filtered to give a bright orange solution of the oxime anion. Glacial acetic acid (~60 mL) was added which resulted in the precipitation of the pale yellow oxime. The crude oxime was isolated by filtration and recrystallised from ethanol/water to yield the pale yellow crystalline *oxime* (32.49 g, 78%). m.p. 130-132 ^{o}C (Lit. m.p. 126-127 ^{o}C), ν_{max} (KBr): 3304, 1605, 1537, 1350, 1216, 1107 cm^{-1}; δ_H(DMSO-d$_6$): 7.81 (2H, d, J = 9.00, *o*-ArH), 8.20 (2H, d, J = 9.00, *m*-ArH), 8.26 (1H, s, CH=N), 11.86 (1H, bs, OH).

4.1.4 *p*-Nitrobenzohydroximoyl chloride[145b] 275



Chlorine gas was bubbled through a cooled (<0 ^{o}C, salt/icebath), stirring solution of *p*-nitrobenzaldoxime (16.68 g, 0.10 mol) in chloroform (500 mL). The solution changed colour from yellow, through green, blue and on to orange and finally yellow. Nitrogen gas was bubbled through the reaction mixture for 4 h to remove excess chlorine gas. The solvent was removed *in vacuo* and the crude chloro-oxime was recrystallised from chloroform/hexane. The *hydroximoyl chloride* (11.62 g, 58%) was isolated by vacuum filtration as a pale yellow crystalline solid, m.p. 124-125 ^{o}C (Lit. 123-124 ^{o}C), ν_{max} (KBr): 3271, 3111, 1599, 1522, 1353, 1335 cm^{-1}; δ_H (DMSO-d$_6$): 8.05 (2H, d, J = 8.78, *o*-ArH), 8.31 (2H, d, J = 8.78, *m*-ArH), 13.01 (1H, bs, OH).

4.1.5 *m*-Nitrobenzaldoxime[209][32] 274

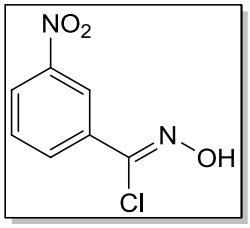


m-Nitrobenzaldehyde (33.31 g, 0.22 mol), hydroxylamine hydrochloride (15.31 g, 0.22 mol), and sodium acetate (36.1 g, 0.4 mol) were heated under reflux for 28 h in 96% ethanol (600 mL). The solvent was evaporated and the resulting yellow residue was dissolved in 2 M NaOH (600 mL) and water (1000 mL). The solution was filtered, leaving a dark yellow solution of the oxime which was acidified with

[32] Reference [209] did not contain a Lit. m.p. for *m*-nitrobenzaldoxime **274**, therefore reference [210] is cited.

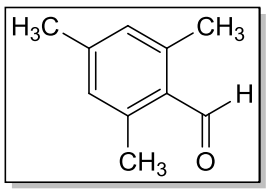
glacial acetic acid (~100 mL) resulting in the precipitation of the oxime. The solid oxime was isolated by filtration, washed with water and recrystallised from ethanol/water to yield the *oxime* (34.75 g, 95%) as a pale yellow crystalline solid, m.p. 115-119 ^{o}C (Lit. m.p. 121-122 ^{o}C),[210] ν_{max} (KBr): 3294, 3069, 1536, 1466, 1350 cm^{-1}; δ_H(DMSO-d$_6$): 7.69 (1H, t, J = 7.95, *m*-ArH), 8.04 (1H, d, J = 7.80, *o*-ArH), 8.20 (1H, m, *p*-ArH), 8.32 (1H, m, *o*-ArH), 8.41 (1H, s, CH=N), 11.68 (1H, s, OH); δ_C: 120.8, 123.6, 130.3, 132.3 (4 x ArCH), 134.9 (*ipso* C of Ar), 146.6 (C-NO$_2$), 148.1 (CH=NOH).

4.1.6 *m*-Nitrobenzohydroximoyl chloride[145b] 276



Chlorine gas was bubbled through a cooled (<0 ^{o}C, salt/ice-bath), mechanically stirred solution of *m*-nitrobenzaldoxime (4.21 g, 25 *m*mol) in chloroform (200 mL). The reaction mixture went from yellow-green-green with precipitate to green/blue to light green and finally yellow. The solution was stirred at room temperature overnight. Nitrogen gas was bubbled through the resulting solution to remove excess chlorine (8 h) in the solution. The solvent was removed *in vacuo* to give a pale yellow solid. Recrystallisation from chloroform:hexane to yield the *hydroximoyl chloride* (3.09 g, 61%) as a yellow crystalline solid, m.p. 97-99 ^{o}C (Lit. 99-100 ^{o}C). ν_{max} (KBr): 3306, 3082, 1698, 1526, 1354 cm^{-1}; δ_H(DMSO-d$_6$): 7.87 (1H, t, J = 8.06, *o*-ArH), 8.31 (1H, m, *o*-ArH), 8.42 (1H, m, *p*-ArH), 8.59 (1H, t, J = 1.97, *m*-ArH), 12.94 (1H, bs, OH). δ_C: 121.3, 125.3, 131.0 and 132.9 (4 x ArCH), 134.0 (*ipso* C of Ar), 134.4 (C-NO$_2$), 148.3 [C(Cl)=NOH].

4.1.7 Mesitaldehyde[145c] 279

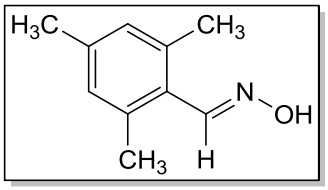


A solution of mesitylene (72.09 g, 0.60 mol) in dry dichloromethane (375 mL) was cooled (<10 ^{o}C, water/ice bath) and $TiCl_4$ (105 mL, 0.96 mol) was added over a period of 3 min. On addition, the solution changed from yellow to orange to brown/orange. While the solution was stirred and cooled, dichloromethylmethyl ether (57.54 g, 0.50 mol) was added dropwise over a 25 min period. The reaction commenced (as indicated by the evolution of gas-HCl) when the first drop of the chloro ether was added. Bubbles were noted in the solution and the solution became red/brown in colour. After the reaction was complete, the solution was stirred for 5 min in the water/ice-bath. The solution was stirred without cooling for 30 min, then heated to 35-40 ^{o}C and stirred for 15 min at this temperature. The solution began to reflux. Once the 15 min had elapsed, the solution was cooled and the deep red solution was transferred to a 1 L separation funnel

which contained ~0.5 kg ice. On addition to the ice, effervescence and a colour change from deep red to white/clear solution were observed. The phases were separated. The aqueous layer was washed with dichloromethane (50 mL) and the organic extracts were combined. Nitrogen gas was used to retard the auto oxidation of the aldehyde in place of hydroquinone. The organic extracts were washed with water (3 x 75 mL), dried and the solvent was evaporated *in vacuo* to yield the *aldehyde* (54.94 g, 74%) as a pale yellow liquid, b.p. 102-112 ^{o}C @ 15 mmHg (Lit. 113-115 ^{o}C @ 11 mmHg); ν_{max} (film): 2922, 1689, 1609, 1437, 1378 cm^{-1}; δ_H: 2.30 (3H, s, *p*-ArC<u>H</u>$_3$), 2.56 [6H, s, *o*-Ar(C<u>H</u>$_3$)$_2$], 6.88 (2H, s, Ar<u>H</u>), 10.54 (1H, s, C<u>H</u>O); δ_C: 21.5 and 21.8 (2 x Ar<u>C</u>H$_3$), 128.9 (*p*-Ar<u>C</u>-CH$_3$), 130.9 (Ar<u>C</u>H), 141.9 [*o*-Ar<u>C</u>-(CH$_3$)$_2$], 144.3 (<u>C</u>-CHO), 193.4 (<u>C</u>HO).

4.1.8 Mesitaldoxime 280

Method 1[14d]33



Hydroxylamine hydrochloride (9.36 g, 0.14 mol) was added to a cooled (<10 ^{o}C, water/ ice-bath), stirring solution of mesitaldehyde (18.04 g, 0.12 mol) in water (32 mL), 95% ethanol (32 mL) and ice (60 mL). 50% Sodium hydroxide solution (25 mL) was added dropwise to the stirring solution of mesitaldehyde and hydroxylamine hydrochloride. Ice (~20 mL) was added to maintain the temperature between 25-30 ^{o}C. The solution was stirred overnight (19 h). The resulting pale creamy yellow solid was dissolved in ether (124 mL). This resulted in a bright orange/brown bi-phasic mixture. The phases were separated and the organic phase was acidified to pH 6 with conc. HCl. The aqueous layer was extracted with dichloromethane (123 mL initially, then 2 x 50 mL). The organic extracts were washed with water (50 mL), dried and the solvent was evaporated *in vacuo*. The resulting white residue was recrystallised from 1:1 ethyl acetate/hexane to yield *the oxime* (8.95 g, 45%) as a pale yellow crystalline solid, m.p. 119-123 ^{o}C (Lit.124-125 ^{o}C).[24d] ν_{max} (KBr): 3252, 2966, 1610, 1444, 1375, 1297, 944 cm^{-1}; δ_H: 2.28 (3H, s, *p*-Ar-C<u>H</u>$_3$), 2.37 [6H, s, *o*-Ar(C<u>H</u>$_3$)$_2$], 6.88 (2H, s, Ar<u>H</u>), 8.34 (1H, bs, O<u>H</u>), 8.41 (1H, s, C<u>H</u>=N); δ_C: 20.2 and 21.5 (2 x Ar-<u>C</u>H$_3$), 126.8 (*p*-Ar<u>C</u>-CH$_3$), 129.7 (Ar<u>C</u>H), 137.9 [*o*-Ar<u>C</u>-(CH$_3$)$_2$], 139.3 (*ipso* <u>C</u> of Ar). 150.2 (<u>C</u>H=N-OH).

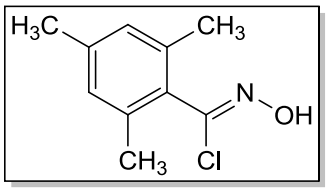
[33] Reference [14d] contained a crude m.p. for mesitaldoxime **280**, therefore the recrystallised m.p. in reference [24d] is cited.

Method 2[208] [34]

Mesitaldehyde (9.00 g, 0.06 mol), hydroxylamine hydrochloride (4.22 g, 0.06 mol), and sodium acetate (12.68 g, 0.16 mol) were heated under reflux in absolute ethanol (166 mL) overnight (24 h). The solvent was evaporated *in vacuo* and the resulting cream coloured residue was dissolved in 2 M NaOH (150 mL) and water (250 mL). The solution was vacuum filtered to give a grey clear solution of the oxime anion. The filtrate was acidified using glacial acetic acid (30 mL) resulting in the precipitation of the cream/white oxime, which was recrystallised from 1:3 ethanol/water to yield *the oxime* (6.4 g, 65%) as a white crystalline solid, m.p. 119-121 ^{o}C (Lit.124-125 ^{o}C).[24d] ν_{max} (KBr): 3249, 2950, 1609, 1444, 1375, 1297, 944 cm^{-1}; δ_H: 2.28 (3H, s, *p*-Ar-C<u>H</u>$_3$), 2.37 [6H, s, *o*-Ar(C<u>H</u>$_3$)$_2$], 6.88 (2H, s, Ar<u>H</u>), 8.03 (1H, bs, O<u>H</u>), 8.41 (1H, s, C<u>H</u>=N); δ_C: 20.2 and 21.5 (2 x Ar-<u>C</u>H$_3$), 126.8 (*p*-Ar<u>C</u>-CH$_3$), 129.7 (Ar<u>C</u>H), 137. 9 [*o*-Ar<u>C</u>(CH$_3$)$_2$], 139.3 (*ipso* <u>C</u> of Ar), 150.3 (<u>C</u>H=N-OH).

4.1.9 2,4,6-Trimethylbenzohydroximoyl chloride 281

Method 1[14d]



A solution of mesitaldoxime (4.90 g, 30 mmol) in chloroform (25 mL) was cooled to 0 ^{o}C (water/icebath). *N*-Chlorosuccinimide (4.01 g, 30 mmol) was added portionwise to the stirring solution at 0 ^{o}C. Once ~$^{1}/_{5}^{th}$ of the overall portion of NCS was added, the solution was monitored for 10 min to see if any temperature increase/exotherm took place. As no increase in temperature took place, 10 mL HCl gas headspace was bubbled through the solution. Chloroform (25 mL) was also added to aid solubility. The remainder of the NCS was then added to the stirring solution while maintaining the reaction temperature at 0 ^{o}C. The solution was stirred for 45 min with icebath in place and overnight at room temperature. Completion of the reaction was indicated by cessation of the exotherm and by formation of no dark colored ring upon application of a small drop of reaction mixture to starch-iodide paper previously moistened with distilled water. The reaction mixture was poured onto ice water (~100 mL) and stirred until homogenous. The phases were separated and the aqueous phase was extracted with chloroform (2 x 50 mL). The organic extracts were combined, dried and concentrated *in*

[34] Reference [208] contained a crude m.p. for mesitaldoxime **280**, therefore the recrystallised m.p. in reference [24d] is cited.

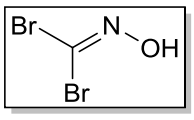
vacuo to yield the crude hydroximoyl chloride as a pale yellow oil. The sample was put on high vacuum line and the *hydroximoyl chloride* (5.7 g, 97%) solidified as a white solid, m.p. 66-74.5 ^{o}C (Lit. m.p. 61-69 ^{o}C); ν_{max} (film): 3294, 2921, 2289, 1707, 1610, 1454, 1423, 961 cm^{-1}; δ_H: 2.29 [6H, s, ArC-(C<u>H</u>$_3$)$_2$], 2.31 (3H, s, ArC-C<u>H</u>$_3$), 6.90 (2H, s, *m*-Ar<u>H</u>), 8.17 (1H, bs, O<u>H</u>).

Method 2[152]35

Pyridine (0.2 mL, 2.8 mmol) was added to a stirring solution of mesitaldoxime (4.90 g, 30 mmol) in chloroform (29 mL) at room temperature. The stirring solution was heated to 40 ^{o}C and *N*-chlorosuccinimide (4.41 g, 33 mmol) was added slowly. The resulting pale yellow solution was left to stir at 40 ^{o}C for 3 h. The solution was cooled to room temperature and dichloromethane (200 mL, distilled) added. The solution was transferred to a separating funnel and washed with water (2 x 100 mL) and brine (1 x 100 mL). The organic extract was dried, filtered and solvent evaporated *in vacuo* to yield the crude hydroximoyl chloride as a pale yellow oil. The sample was placed under high vacuum to remove residual solvent and the *hydroximoyl chloride* (5.38 g, 91%) was isolated as a pale yellow solid, m.p. 59-65 ^{o}C (Lit. 61-69 ^{o}C) [14d]; ν_{max} (KBr): 3294, 2921, 1706, 1611, 1444, 1423, 962 cm^{-1}; δ_H: 2.26 [6H, s, *o*-Ar(C<u>H</u>$_3$)$_2$], 2.28 [3H, s, *p*-Ar(C<u>H</u>$_3$)], 6.87 (2H, s, *m*-Ar<u>H</u>), 8.67 (1H, bs, O<u>H</u>).

4.2 Synthesis of dihaloformaldoximes

4.2.1 Dibromoformaldoxime 41



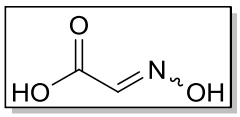
Solid hydroxylamine hydrochloride (13.90 g, 0.20 mol) was added to a stirring solution of glyoxylic acid monohydrate (18.42 g, 0.20 mol) in water (120 mL) at room temperature and the resulting clear solution was stirred overnight (69 h). Sodium bicarbonate (35.30 g, 0.42 mol) was added carefully to the stirring solution followed by dichloromethane (120 mL, distilled). The solution was then cooled to 0 ^{o}C (water/icebath) and bromine (14.5 mL, 0.30 mol) was added dropwise *via* pressure-equalising addition funnel at such a rate that the temperature did not exceed 10 ^{o}C. The pale orange solution was then warmed to room temperature and stirred overnight. The phases were separated and the aqueous phase was washed with dichloromethane (190 mL, distilled), organic extracts combined, dried and solvent removed *in vacuo* to yield

[35] Method of preparation adapted from reference[152]. Reference [14d] is used for the lit. m.p. comparison.

crude *dibromformaldoxime* (17.98 g, 44%) as a white crystalline solid, m.p. 55.5-60 ^{o}C (Lit. m.p. 63-65 ^{o}C).[35] ν_{max} (KBr): 3172, 1588, 1401, 982, 905 cm^{-1}; δ_C: 99.2 (C=NOH).

4.2.2 Glyoxylic acid aldoxime 283

Method 1



Glyoxylic acid monohydrate (10.18 g, 0.11 mol), hydroxylamine hydrochloride (7.68 g, 0.11 mol) and sodium acetate (18.04 g, 0.22 mol) were heated under reflux for 24 h in 95% ethanol (300 mL). The solvent was removed *in vacuo* and the resulting white residue was dissolved in a mixture of 2 M NaOH (300 mL) and water (500 mL). The resulting bright yellow solution of the oxime anion was acidified with glacial acetic acid. At pH 4, the oxime had not precipitated out so the yellow solution was stirred overnight. The solution was extracted with ether (500 mL first, then 2 x 200 mL). The organic extracts were combined, dried and the solvent was evaporated *in vacuo* to yield the *glyoxylic acid aldoxime* (0.251 g, 3%) as a pale cream solid, m.p. 90-97 ^{o}C (Lit. m.p. 134-136 ^{o}C).[145i] ν_{max} (KBr): 3199, 1719, 1627, 1459, 1257 cm^{-1}: δ_H(DMSO-d_6): 7.46 (1H, s, CH=N).

Method 2

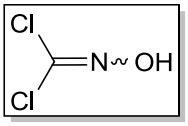
Hydroxylamine hydrochloride (7.57 g, 0.11 mol) was added to a stirring solution of glyoxylic acid monohydrate (10.01 g, 0.11 mol) in water (100 mL) and the resulting solution was stirred until homogenous. The solution was then basified (alkaline to litmus) with 1 M aqueous NaOH solution. This solution was then stirred for 69 h. The solution was acidifed with 10% (v/v) aqueous sulphuric acid solution [red to litmus] and the oxime was extracted with ether (3 x 100 mL). The combined organic extracts were dried and solvent removed *in vacuo* to yield the *oxime* (50 mg, 5%) as a pale cream solid, m.p. 107-110 ^{o}C (Lit. m.p. 134-136 ^{o}C).[145i] ν_{max} (KBr): 3198, 1719, 1459, 1256, 1008 cm^{-1}; δ_H(D_2O): 7.58 (1H, s, CH=N); δ_C(D_2O): 142.9 (CH=N), 165.8 (COOH).

Method 3

Hydroxylamine hydrochloride (13.58 g, 0.195 mol) was added to a stirring solution of glyoxylic acid monohydrate (18.02 g, 0.196 mol) in water (200 mL) at room temperature. Once the clear mixture was homogenous, it was basified (from pH 1) to pH 10 and stirred overnight. The solution was concentrated to a quarter of its original volume and some solid precipitated. The mixture was extracted with ether (3 x 200 mL) and the combined organic

extracts were dried, filtered and solvent was removed *in vacuo* to yield a white solid. Granular salt was added to the aqueous phase and the solution was stirred overnight. The aqueous phase was then extracted with ether (3 x 200 mL). A white emulsion formed. The combined organic extracts were dried, filtered and the solvent removed *in vacuo* to yield the *oxime* (13.59 g, 78%) as a white solid, m.p. >304 ^{o}C (without melting) (Lit. m.p. 134-136 ^{o}C).[145i] ν_{max} (KBr): 3272, 1701, 1451, 1253, 1026 cm^{-1}; δ_C(D_2O): 143.1 (CH=NOH), 165.9 (COOH).

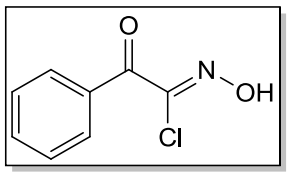
4.2.3 Dichloroformaldoxime[145i] 16



N-Chlorosuccinimide (1.34 g, 10.00 mmol) and glyoxylic acid aldoxime (0.46 g, 5.19 mmol) in chloroform (5 mL) were heated under reflux at 70 ^{o}C until effervescence ceased. The solvent was evaporated *in vacuo* to yield the crude *oxime* (1.67 g, >100%) as a white solid. The sample was used directly in the next step without further purification or analysis.

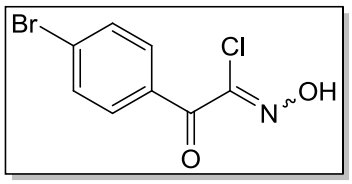
4.3 Synthesis of 1-aroyl-1-chloroformaldoximes

4.3.1 1-Benzoyl-1-chloroformaldoxime[145d] 286



Acetophenone (22.50 g, 0.19 mol) in water (40 mL) was combined with 37% HCl (30 mL, 0.4 mol) at room temperature and the solution was stirred. Sodium nitrite (0.50 g, 7.3 mmol) was then added portionwise to the stirring solution. The resulting reaction mixture was heated to 70 ^{o}C and conc. nitric acid (12 mL) was added dropwise to the stirring solution over 1.8 h. The resulting solution was then stirred for 1.3 h at 70 ^{o}C. A sticky yellow oily residue separated from the mixture which solidified on cooling. This solution was left to stand overnight. This solid was isolated by extraction with dichloromethane (3 x 100 mL). The combined organic extracts were dried, filtered and solvent removed *in vacuo* to yield the crude *chloro-oxime* (26.46 g, 77%) as a yellow solid, m.p. 128-131 ^{o}C (Lit. 130-131 ^{o}C). ν_{max} (KBr): 3277, 1660, 1448, 1392, 1039, 854, 720 cm^{-1}; δ_H(DMSO-d_6): 7.47 (2H, m, *m*-ArH), 7.62 (1H, m, *p*-ArH), 7.97 (2H, m, *o*-ArH), 9.21 (1H, bs, OH); δ_C(DMSO-d_6): 128.4, 130.7 and 133.8 (3 x ArCH), 134.8 (*ipso* C of Ar), 139.2 [C(Cl)=NOH] and 183.9 (C=O).

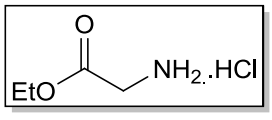
4.3.2 1-(*p*-Bromobenzoyl)-1-chloroformaldoxime 292



Sodium nitrite (0.10 g, 1.51 mmol) was added to a stirring solution of 4-bromoacetophenone (7.92 g, 39.78 mmol) and conc. HCl (37%, 7.5 mL, 90 mmol) in water (10 mL) at room temperature. The solution was stirred and heated to 70 ^{o}C. Nitric acid (3 mL, 0.07 mol) in water (5 mL) was added dropwise *via* pressure-equalising addition funnel at 70 ^{o}C. Following addition, the stirring solution was maintained at 70 ^{o}C for 64 h. Chloroform (100 mL) was added to dissolve the yellow sticky solid which had separated from the solution. Water (20 mL) was also added as an emulsion formed. The solution was transferred to separating funnel and the phases were separated. The aqueous phase was extracted with chloroform (1 x 100 mL). The organic phase was then washed with water (1 x 50 mL). The organic extracts were dried, filtered and concentrated to ~50 mL. Hexane (~100 mL) was added and the solution left to stand overnight. The *hydroximoyl chloride* (1.8 g, 17%) was isolated as a pale yellow solid by vacuum filtration, m.p. 125-127 ^{o}C. Found: C, 37.10; H, 1.96; N, 5.13 $C_8H_5NO_2BrCl$ requires C, 36.92; H, 1.94; N, 5.43%; ν_{max} (film): 3284, 1668, 1596, 1581, 1425, 1039 cm^{-1}; δ_H: 7.62 (2H, m, Ar<u>H</u>), 7.88 (2H, m, Ar<u>H</u>), 8.83 (1H, bs, O<u>H</u>); δ_C: 129.3 [Ar<u>C</u>(Br)], 131.7 and 132.1 (2 x Ar<u>C</u>H), 133.4 (*ipso* <u>C</u> of Ar), 139.4 [<u>C</u>(Cl)=NOH], 182.6 (<u>C</u>=O). m/z = no identifiable ions.

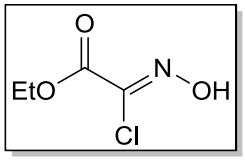
4.4 Synthesis of other hydroximoyl halides

4.4.1 Glycine ethyl ester hydrochloride[24a] 294

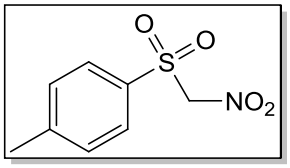


HCl gas was bubbled through a mechanically stirred suspension of glycine (75.1 g, 1.0 mol) in 96% ethanol (300 mL). A further portion of 96% ethanol (200 mL) was added to aid stirring of the mixture. The mixture was heated under reflux overnight (19 h). The mixture was cooled and the solvent was evaporated *in vacuo* to yield *glycine ethyl ester hydrochloride* (131 g, 94%) as a white solid, m.p. 120-122 ^{o}C (Lit. 144 ^{o}C). ν_{max} (KBr): 2977, 1745, 1508, 1413, 1248 cm^{-1}; δ_H(D_2O): 1.19 (3H, t, J = 7.20, $C\underline{H}_3CH_2O$), 3.81 (2H, s, $COC\underline{H}_2NH_2$.HCl), 4.20 (2H, q, J = 7.00, $CH_3C\underline{H}_2O$); δ_C: 13.5 ($\underline{C}H_3CH_2O$), 40.5 ($CO\underline{C}H_2NH_2$.HCl), 63.5 ($CH_3\underline{C}H_2O$), 168.5 [$O\underline{C}(O)CH_2$].

4.4.2 Ethylchloroglyoxalate oxime[157] 295



Concentrated hydrochloric acid (20.75 mL, 0.21 mol) was added dropwise to a cooled (<0 ^{o}C, salt/ice-bath), stirring solution of glycine ethyl ester hydrochloride (35.04 g, 0.25 mol) in water (47.5 mL). The mixture was cooled (<0 ^{o}C, salt/ice bath) and sodium nitrite (17.5 g, 0.3 mol) in water (25 mL) was added dropwise over 1 h. The solution turned from yellow to green and evolution of gas was observed. Further conc. hydrochloric acid (20.75 mL, 0.2 mol) was added followed by additional sodium nitrite (17.5 g, 0.3 mol) in water (25 mL) dropwise over 1 h. The reaction colour went from pale green through blue/green, brown/orange and finally to orange. A brown gas evolved on addition of sodium nitrite. The reaction was stirred for 69 h. Saturated sodium chloride solution (50 mL) was added to the cloudy mixture. The product was extracted into dichloromethane (4 x 50 mL), the organic extracts were combined, dried and the solvent evaporated *in vacuo*. The resulting residue was recrystallised from chloroform/hexane to yield *the hydroximoyl chloride* (9.0 g, 24%) as a colourless crystalline solid, m.p. 80-81 ^{o}C (Lit. 80 ^{o}C). ν_{max} (KBr): 3310, 1751, 1618, 1457, 1307 cm^{-1}; δ_H: 1.39 (3H, t, J = 7.15, C<u>H</u>$_3$CH$_2$O), 4.40 (2H, q, J = 7.14, CH$_3$C<u>H</u>$_2$O), 9.66 (1H, bs, O<u>H</u>). δ_C: 14.4 (<u>C</u>H$_3$CH$_2$O), 64.1 (CH$_3$<u>C</u>H$_2$O), 133.4 (<u>C</u>=NOH), 159.0 (<u>C</u>=O).

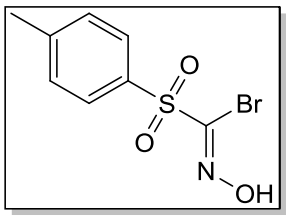


4.4.3 *p*-Toluenesulfonylnitromethane 297

Sodium metal (4.14 g, 0.18 mol) was reacted with dry methanol (75 mL) and the excess methanol was evaporated *in vacuo*. DMF (180 mL) was added and the resulting solution was cooled in an icebath (<10 ^{o}C, water/icebath). Nitromethane (10 mL, 0.19 mol) was added and a cloudy white mixture resulted. Following 40 min of stirring the cooled reaction mixture, sodium *p*-toluenesulfinate (16.04 g, 0.09 mol), followed by iodine (20.31 g, 0.08 mol) were added to the stirring solution. The resulting bright orange solution was stirred overnight at room temperature. The reaction mixture was poured onto icewater (~600 g) and the solution was stirred until the ice had melted. Solid sodium sulphite was added until the mixture became lighter in colour. The excess solid sodium sulphite was removed by filtration. The filtrate was then acidified to pH 1-3 with 2.4 M HCl. A precipitate formed which was isolated by vacuum filtration. Recrystallisation from 95% ethanol yielded *p-toluenesulfonylnitromethane* (7.65 g, 40%) as a pink/orange solid, m.p. 115-116 ^{o}C (Lit. m.p. 116 ^{o}C[160]). ν_{max} (KBr): 3018, 2952, 1551, 1385, 1327, 1153 cm^{-1}; δ_H: 2.50 (3H, s,

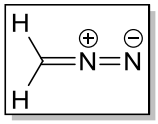
ArC$\underline{H}_3$), 5.57 (2H, s, C$\underline{H}_2NO_2$), 7.44 (2H, d, J = 7.96, *o*-Ar$\underline{H}$), 7.84 (2H, m, *m*-Ar$\underline{H}$); δ_C: 21.9 [ArC($\underline{C}H_3$)], 90.4 ($SO_2\underline{C}H_2NO_2$), 128.4 and 130.4 (2 x Ar$\underline{C}$H), 132.6 [*p*-Ar$\underline{C}$(CH_3)], 147.2 (*ipso* $\underline{C}$ of Ar). m/z = 214 ($M\text{-}H^+$, 100%).

4.4.4 1-*p*-Toluenesulfonyl-1-bromoformaldoxime[51b] 299



A solution of bromine (1.1 mL, 20 mmol) in dry dichloromethane (35 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of sodium acetate (7.4 g, 90 mmol) and *p*-toluenesulfonylnitromethane (4.31 g, 20 mmol) in dichloromethane (70 mL, dry). A white solid precipitated from the solution. The reaction mixture was washed with water (1 x 30 mL), the phases were separated and the organic phase was dried, filtered and concentrated. ^1H NMR spectroscopic analysis conducted at this point to ascertain the level of bromination - predominantly mono-bromo product isolated. A cold (<0 ^oC, salt/icebath), stirring solution of the crude bromination product in ether (62.5 mL) was treated with ethereal diazomethane (~1.0 g, 24.5 mmol, added in 3 portions). On addition, the solution changed from clear to yellow and effervescence was observed, then the solution became clear and the next portion was added. After 10 min, the solution was partially evaporated under reduced pressure (~20 mL solution) to remove excess diazomethane. The residue was dissolved in dichloromethane (37.5 mL, dry) and stirred, then heated at reflux for 15 min. The solvent was removed *in vacuo* and to the resulting orange oil was added dry dichloromethane (~5 mL) and distilled hexane (~5 mL). This solution was then transferred to a freezer. The *hydroximoyl bromide* (4.29 g, 77%) that crystallised was isolated as a yellow solid by vacuum filtration, m.p. 101-104 ^oC (Lit. m.p. 126.5-127.5 ^oC).[18b] ν_{max} (film): 3088, 2971, 2912, 2866, 1588, 1571, 1344, 1326, 1300, 1156 cm^{-1}; δ_H: 2.48 (3H, s, Ar-C$\underline{H}_3$), 7.40 (2H, d, J = 8.01, *o*-Ar$\underline{H}$), 7.89 (2H, d, J = 8.38, *m*-Ar$\underline{H}$), 9.47 (1H, bs, O$\underline{H}$); δ_C: 21.8 [ArC($\underline{C}H_3$)], 129.7 and 130.3 (2 x Ar$\underline{C}$H), 132.4 [*p*-Ar$\underline{C}$(CH_3)], 132.6 (*ipso* $\underline{C}$ of Ar), 146.6 [$\underline{C}$(Br)=N].

4.4.5 Diazomethane[161] 298



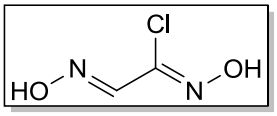
Diazald® (*N*-methyl-*N*-nitroso-*p*-toluenesulfonylamide) (7.51 g, 35 mmol) in ether (43.5 mL) was added dropwise over 1 h to a solution of potassium hydroxide (2.81 g, 50 mmol) in 96% ethanol (11.5 mL) and water (2.8 mL) while stirring at 70 ^oC. The rate of addition was regulated so that the addition of one drop of Diazald® coincided with the distillation of one drop of diazomethane. Once the addition

was complete, further ether (20 mL) was added and the distillation was continued until most of the ether had distilled across, to give a solution of diazomethane in ether (~1.0 g, 25 mmol) which was used directly in the next step. The solution was yellow in colour.

Note/caution: Diazomethane is highly toxic and explosive. Its preparation should be carried out in a well-ventilated fume-hood with adequate shielding. Explosive decomposition of diazomethane can be initiated by sharp surfaces, thus only glassware with clear-seal® joints should be used for the distillation. The distillation apparatus should not be exposed to strong sun or artificial light.

4.4.6 Chloroglyoxime 303

Method 1[211]36



A saturated solution of sodium carbonate (15.92 g, 0.15 mol) in water (60 mL) was added portionwise to a cooled (<0 °C, salt/icebath), stirring solution of hydroxylamine hydrochloride (20.91 g, 0.30 mol) in water (50 mL). A clear pink solution resulted and anhydrous chloral (14.73 g, 0.10 mol) was added dropwise *via* a Pasteur pipette to the cooled (<0 °C, salt/icebath) stirring solution. On addition of some of the chloral, effervescence was observed and a gloupy layer appeared on surface of the solution. This solution was not stirring successfully, so addition was stopped until the solution was stirring properly. This was done every time the solution became too gloopy and continued until chloral addition was complete. The resulting pale yellow cloudy mixture was stirred for 2 h. (The icebath was not in place during the stir time but the solution remained cold). The icebath (<0 °C, salt/icebath) was reinstated prior to NaOH addition. A saturated solution of sodium hydroxide (16.07 g, 0.4 mol) in water (50 mL) was then added portionwise to the freshly cooled stirring solution. The resulting yellow solution was stirred for 1.25 h. This stirring, cooled (<0 °C, salt/icebath) solution was neutralised with 10% (v/v) aq. H_2SO_4 to pH 7. At pH 7, a pale yellow solid precipitated from the mixture. This precipitate was isolated by vacuum filtration and dissolved in diethyl ether. This solution was then concentrated to a third of its original volume *in vacuo*. Hexane was added to precipitate the crude oxime (2.00 g, 16%). m.p. 156-158 °C (Lit. 158-159 °C),[163] ν_{max} (KBr): 3288, 1678, 1618, 1471, 1272, 982 cm^{-1}; δ_H(DMSO-d_6): 8.34 (1H, s, C<u>H</u>=N), 10.36 (1H, bs, O<u>H</u>), 12.31 (1H, bs, O<u>H</u>); δ_C(DMSO-d_6): 137.1 (N=<u>C</u>H), 142.4 [N=<u>C</u>(Cl)].

[36] Reference [211] did not contain a Lit. m.p. for chloroglyoxime **303**.

Method 2

Chloral oxime (8.95 g, 55 mmol), hydroxylamine hydrochloride (3.83 g, 55 mmol) and sodium acetate (9.03 g, 0.11 mol) were heated under reflux for 26 h in 95% ethanol (150 mL). The mixture was cooled and the solvent was removed *in vacuo*. The resulting residue was dissolved in a mixture of 2 M NaOH (150 mL) and water (250 mL). The bright orange solution was then acidified to pH 3 with glacial acetic acid. No precipitate was isolated. The yellow solution was left to stir over the weekend. The pH was found to be pH 4 on checking. The solution was extracted with ether (500 mL first, then 2 x 200 mL). The combined organic extracts were dried, filtered and solvent evaporated *in vacuo*. (2.09 g, 31%) unidentifiable mixture.

Method 3

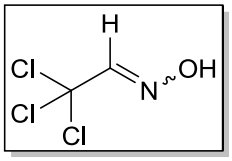
A solution of sodium bicarbonate (15.88 g, 0.19 mol) in water (100 mL) was added portionwise to a stirring solution of hydroxylamine hydrochloride (20.87 g, 0.30 mol) in water (50 mL). Once effervescence had subsided, chloral hydrate (16.55 g, 0.10 mol) was added portionwise to the stirring clear solution and the solution was stirred overnight. The solution was concentrated to dryness and a further portion of water (75 mL) added. The solution was cooled (<0 ^{o}C, salt/icebath) and a solution of NaOH (16.00 g, 0.40 mol) in water (75 mL) was added portionwise, resulting in a yellow solution. The solution (pH 10) was acidified with 25% sulfuric acid solution. At pH 7, a solid precipitated from the solution and was isolated by vacuum filtration and the filtrate was further acidified to pH 3. Ether (200 mL) was added to the stirring solution and the solution was stirred overnight. The phases were separated and the aqueous phase was extracted with ether (200 mL). The combined organic extracts were dried, filtered and solvent evaporated *in vacuo* to yield a pale yellow solid (2.84 g). Both samples were analysed and the solid isolated at pH 7 was found to be the chloroglyoxime (4.20 g, 34%) as a white solid, m.p. 152-154 ^{o}C (Lit. m.p. 158-159 ^{o}C)[163]. ν_{max} (KBr): 3289, 1678, 1618, 1471, 1272, 983 cm^{-1}; δ_H(DMSO-d$_6$): 8.33 (1H, s, N=C<u>H</u>), 12.37 (1H, bs, OH), 12.58 (1H, bs, OH); δ_C(DMSO-d$_6$): 137.08 (N=<u>C</u>H), 142.43 [N=<u>C</u>(Cl)].

Method 4[162]

To a dried 1 L 3-necked rbf equipped with a thermometer, stirring pellet and dropping funnel protected under nitrogen was added water (60.6 g) and hydroxylamine

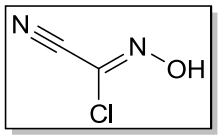
hydrochloride (31.51 g, 0.45 mol). The reaction mixture was stirred at 20-25 ^{o}C for 0.5 h until the solids were dissolved. To the solution was added dropwise, a clear solution of potassium carbonate (31.35 g, 0.23 mol) and water (280 mL) over 55 min at 20-25 ^{o}C, followed by chloral hydrate (25.02 g, 0.15 mol) in portions at 20-28 ^{o}C. After addition, the reaction mixture was stirred overnight and reaction deemed complete by TLC. The reaction mixture was cooled to 0-5 ^{o}C, 25% sodium hydroxide (96.74g, 0.63 mol) was added over 1 h at 0-5 ^{o}C. After addition, the stirring mixture was acidified with 25% sulphuric acid at 0-5 ^{o}C until pH 3.0. The resulting mixture was extracted with methyl-*t*-butyl ether (2 x 37.5 ml). The combined organic layer was dried with sodium sulphate (10.01 g), filtered and then concentrated in vacuo to ~15 g, which was diluted with *n*-heptane (26.70 g). The resulting mixture was concentrated *in vacuo* to ~15 g. To the resulting slurry, was added *n*-heptane (26.70 g), and then cooled to 0-5 ^{o}C and maintained at this temperature over 69 h. The sample was isolated by vacuum filtration and washed with *n*-heptane (2 x 3.65 ml). The sample was dried under high vacuum at 30-38 ^{o}C to yield the chloroglyoxime (3.69 g, 20%) as a white solid, m.p. 154 ^{o}C (Lit. m.p. 158-159 ^{o}C).[163] ν_{max} (KBr): 3270, 1621, 1450, 1273, 1196, 1036, 959 cm^{-1}; δ_H(DMSO-d_6): 8.33 (1H, s, HC=N), 12.31 (1H, bs, OH), 12.52 (1H, bs, OH); δ_C(DMSO-d_6): 137.15 (N=CH), 142.49 [N=C(Cl)]. m/z: 121 (M-H$^+$).

4.4.7 Chloral oxime[164] 305



A solution of anhydrous chloral (**306**) (29.48 g, 0.20 mol), hydroxylamine hydrochloride (6.96 g, 0.10 mol) and calcium chloride (22.21 g, 0.20 mol) in water (20 mL) were stirred together for ~20 min at room temperature and then heated for 1 h at 50 ^{o}C. The solution was then distilled at water aspirator pressure and the fraction collected boiled at 41-44.5 ^{o}C @20 mmHg (Lit. b.p. 82-83 ^{o}C @14 mmHg[164]) correlates with the *product* (31.11 g, 32%). Anhydrous chloral **306** and chloral oxime **305** were obtained in a ratio of 3:1. ν_{max} (film): 3395, 2175, 1715, 1633, 1402, 1300, 1096, 987, 833 cm^{-1}; δ_H: 7.82 (1H, s, CH=N), 8.37 (1H, bs, OH), 9.05 (3H, s, CHO **306**); δ_C: 94.1 (CCl_3 **306**), 103.4 (CH=N **305**), 149.8 (CCl_3 **305**), 176.7 (CHO **306**).

4.4.8 Cyanoformohydroximoyl chloride[157] 304

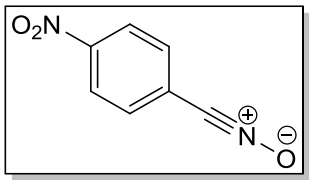


Neat thionyl chloride (7.5 mL, 0.1 mol) was dropwise *via* pressure equalising addition funnel to a stirring solution of chloroglyoxime (3.0 g, 25 mmol) in ether (20mL) under a nitrogen atmosphere. The resulting clear yellow solution was stirred for 80 min at room temperature and the excess $SOCl_2$ and ether were evaporated *in vacuo*. The resulting yellow oily residue was purified by distillation (b.p. 72 ^oC @ 15 mmHg) and the distillate solidified on standing. The distillate was recrystallised from hexane and placed in the freezer. The solvent was evaporated *in vacuo* as the *hydroximoyl halide* (0.8 g, 31%) was a white needle-like crystalline solid at -20 ^oC and a pale yellow oil at room temperature*;* ν_{max} (film): 3234, 2990, 2866, 2243, 1624, 1459, 1146, 1113, 1049cm^{-1}; δ_C: 111.1 (C≡N) and 115.2 [C(Cl)=N]. m/z: 103 (M-, 100%).

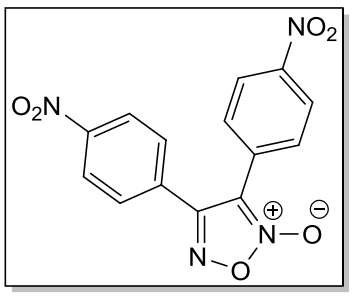
5 Preparation of nitrile oxides

5.1.1 *p*-Nitrobenzonitrile-*N*-oxide 265

NMR Spectroscopy tube reaction



A solution of *p*-nitrobenzohydroximoyl chloride (20.10 mg, 0.105 mmol) in chloroform-d (1.5 mL) and a solution of triethylamine (15.00 mg, 0.148 mmol) also in chloroform-*d* (1.5 mL) were combined. A 0.6 mL portion of this solution was transferred to an NMR tube and sample submitted for ^1H and ^{13}C NMR spectroscopic analysis. δ_H: 7.73 (2H, m, ArH), 8.31 (2H, m, ArH); δ_C: 119.6 (C≡N), 123.4 and 132.1 (2 x ArCH). The sample was monitored over time to view the dimerisation of the nitrile oxide.

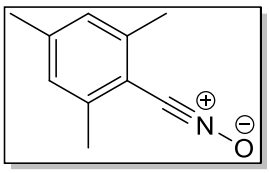


312

δ_H: (t = 15 h): 7.90 (3H, m, ArH **312**), 8.32 (5H, m, ArH **312**). Dimerisation of the nitrile oxide **265** to the furoxan **312** was complete within 15 h.

Method 2[145l]

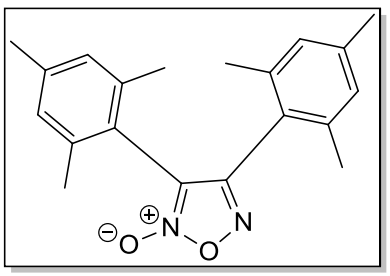
Triethylamine (0.84 mL, 6.03 mmol) was added dropwise to a cooled (<0 °C, salt/icebath), stirring solution of *p*-nitrobenzohydroximoyl chloride (1.01 g, 5.04 mmol) in the minimum amount of ethanol. Cold water (~10 mL) was then added. The resulting solution was filtered by vacuum filtration and was washed with water (~5 mL). The *nitrile oxide* (0.75 g, 91%) was isolated as a pale yellow solid, m.p. 92-93 °C (Lit m.p. 95 °C). δ_H: Exp 10 15:59 13.04.2010, 7.72 (2H, m, ArH **265**), 8.31 (2H, m, ArH **265**) shows nitrile oxide. Exp 11 17:14 13.04.2010 7.73 (2H, m, ArH **265** & **312**), 8.33 (2.22H, m, ArH **265** & **312**) shows some dimer beginning to form, but predominantly nitrile oxide. Exp 12 09:44 14.04.2010 shows the dimer-no nitrile oxide. 7.73 (4H, m, ArH **312**), 8.34 (4H, m, ArH **312**).



5.1.2 Mesitonitrile-*N*-oxide 7

2,4,6-Trimethylbenzohydroximoyl chloride (304.80 mg, 1.54 mmol) in ether (10 mL) was added dropwise (*via* Pasteur pipette) to a stirring solution of triethylamine (155.30 mg, 1.52 mmol) in ether (10 mL) at room temperature. The resulting white cloudy mixture was stirred at room temperature for 2 h and filtered. The solvent was removed *in vacuo* to yield the crude *mesitonitrile-N-oxide* (0.260 g, >100%[37]) as a white crystalline solid, m.p. 92-93 °C (Lit. 110-112 °C).[14d] ν_{max} (film): 2948, 2919, 2288, 1332 cm^{-1}; δ_H: 2.30 (3H, s, ArC$\underline{H}_3$), 2.42 [6H, s, Ar(C$\underline{H}_3$)$_2$], 6.91 (2H, s, Ar$\underline{H}$); δ_C: 20.8 [Ar($\underline{C}H_3$)$_2$], 21.4 (Ar$\underline{C}H_3$), 111.0 [Ar$\underline{C}$(CH$_3$)$_2$], 128.3 (Ar$\underline{C}$H), 141.0 (*ipso* $\underline{C}$ of Ar), 141.7 ($\underline{C}$≡N).

Complete dimerisation to furoxan **313** was observed (in $CDCl_3$) within 15 days. δ_H: 2.25 (3H, s, ArC$\underline{H}_3$), 2.28 [6H, s, Ar(C$\underline{H}_3$)$_2$], 2.31 (3H, s, ArC$\underline{H}_3$), 2.42 [6H, s, Ar(C$\underline{H}_3$)$_2$], 6.84 (2H, s, Ar$\underline{H}$), 6.90 (2H, s, Ar$\underline{H}$); δ_C: 18.6 [Ar($\underline{C}H_3$)$_2$], 20.8 [Ar($\underline{C}H_3$)$_2$], 21.4 (Ar$\underline{C}H_3$), 128.3 (Ar$\underline{C}$H), 128.7 (Ar$\underline{C}$H), 132.7 ($\underline{C}$=N), 135.1 ($\underline{C}$=N), 141.0 (*ipso* $\underline{C}$ of Ar), 141.7 (*ipso* $\underline{C}$ of Ar).

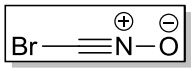


313

[37] Contains ether.

5.1.3 Bromoformonitrile-*N*-oxide 13

Method 1



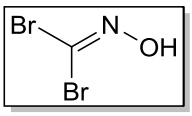
Dibromoformaldoxime (0.61 g, 3.01 mmol) in ether (5 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of triethylamine (0.31 g, 3.02 mmol) in ether (5 mL). Ether (10 mL) was used to rinse the flask and the solution was stirred for ~2 min. The mixture was filtered to remove the precipitate and the solvent was evaporated *in vacuo* to yield the nitrile oxide (0.187 g, 51%) as a white solid. δ_C: 98.2 (Br-C≡N).

Method 2: NMR Spectroscopy tube reaction

Dibromoformaldoxime (14.2 mg, 0.07 mmol) was dissolved in 0.07 M triethylamine solution (1 mL, $CDCl_3$) and the resulting mixture was monitored over time by ^{13}C NMR spectroscopy. δ_C: Exp 10: 99.08 (C≡N, **13**), 114.29. Exp 12: [7 days after addition] 98.92, 99.02 (2 x C=N, **15**).

Method 3: NMR spectroscopy tube reaction

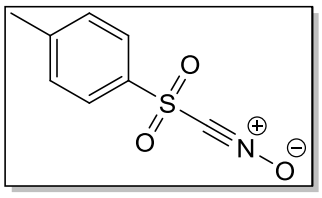
Dibromoformaldoxime (42.6 mg, 0.21 mmol) was dissolved in $CDCl_3$ (0.7 mL) and ^{13}C NMR spectroscopic analysis was carried out. Triethylamine (44 µl, 0.316 mmol) was added directly to the NMR spectroscopy tube and ^{13}C NMR submitted. δ_C: 95.91 (C=N, **41**), 104.0, 111.4, 124.8.



41

5.1.4 *p*-Toluenesulfonylformonitrile-*N*-oxide 307

Method 1: NMR spectroscopy tube reaction

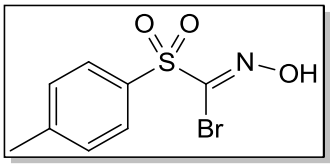


1-*p*-Toluenesulfonyl-1-bromoformaldoxime (19.90 mg, 0.07 mmol) was dissolved in $CDCl_3$ (1.5 mL) and combined with triethylamine (8.90 mg, 0.09 mmol) and the resulting solution was shaken to ensure dissolution. 0.6 mL of this solution was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out. δ_H: 1.44 (15.6H, t, C$\underline{H}_3$ **433**), 2.47 (3.28H, s, ArC$\underline{H}_3$ **309**), 2.49 (3.83H, s, ArC$\underline{H}_3$ **307**),

2.52 (3.32H, s, ArC<u>H</u>$_3$ **309**), 3.17 (23.4H, m, C<u>H</u>$_2$ **433**), 7.38 (2.52H, d, J = 8.12, Ar<u>H</u> **307**), 7.45 (4.5H, m, Ar<u>H</u> **309**), 7.85 (2.03H, d, J = 8.28, Ar<u>H</u> **307**), 8.04 (4H, dd, J = 8.9, 2.6, Ar<u>H</u> **309**). A mixture of triethylamine hydrobromide (**433**), nitrile oxide (**307**) and furoxan (**309**) was observed in a ratio of 2.6:1:1.

Method 2

1-*p*-Toluenesulfonyl-1-bromoformaldoxime (834.60 mg, 3.00 mmol) in ether (10 mL) and triethylamine (308.80 mg, 3.05 mmol) in ether (5 mL) were combined at room temperature. A cloudy pale yellow mixture resulted which was stirred for ten minutes. The mixture was filtered and the solvent was evaporated *in vacuo* to yield a pale yellow solid (0.38 g, 64%). δ_H: 2.48 (6.91H, s, ArC<u>H</u>$_3$ **299**), 2.49 (4.11H, s, ArC<u>H</u>$_3$ **309**), 2.51 (2.99H, s, ArC<u>H</u>$_3$ **307**), 2.54 (3.58H, s, ArC<u>H</u>$_3$ **309**), 7.32 (1.32H, d, J = 7.97, Ar<u>H</u>), 7.39 (5.26H, d, J = 7.97, Ar<u>H</u> **299**), 7.44 (4.88H, m, Ar<u>H</u> **309**), 7.51 (2.14H, d, J = 8.02, Ar<u>H</u>), 7.81 (1.44H, m, Ar<u>H</u>), 7.88 (4.38H, m, Ar<u>H</u> **299**), 7.96 (2.48H, d, J = 8.48, Ar<u>H</u>), 8.04 (4.04H, dd, J = 2.17, 8.48 Ar<u>H</u> **309**).



299

Method 3

Solid potassium hydrogencarbonate (0.107 g, 1.069 mmol) was added to a stirring solution of 1-*p*-toluenesulfonyl-1-bromoformaldoxime (0.280 g, 1.01 mmol) in chloroform (10 mL) at room temperature. The resulting solution was stirred for 5 min and water (5 mL) was added. The phases were separated and organic phase dried, filtered and solvent removed *in vacuo* to yield a grey solid (0.241 g). δ_H: Predominantly **299** was isolated with a trace of **307**/**309**. *<u>Dehydrohalogenation using potassium hydrogencarbonate was not successful with this reaction time</u>*.

Method 4

Solid potassium carbonate (0.141 g, 1.02 mmol) was added to a stirring solution of 1-*p*-toluenesulfonyl-1-bromoformaldoxime (0.280 g, 1.01 mmol) in chloroform (10 mL) at

room temperature. The resulting solution was stirred for 5 min and water (5 mL) was added. The phases were separated and organic phase dried, filtered and solvent removed *in vacuo* to yield a clear oil (0.12 g). δ_H: 2.46 (2.91H, s, ArC<u>H</u>$_3$ **309**), 2.49 (3.36H, s, ArC<u>H</u>$_3$ **307**), 2.51 (3.01H, s, ArC<u>H</u>$_3$ **309**), 7.38 (2.02H, d, J = 8.04, Ar<u>H</u> **307**), 7.44 (4.14H, m, Ar<u>H</u> **309**), 7.88 (2H, d, J = 8.37, Ar<u>H</u> **307**), 8.04 (3.77H, m, Ar<u>H</u> **309**).

Method 5

1,8-Diazabicyclo-[5.4.0]-undec-7-ene (0.15 mL, 1.0 mmol) was added to a stirring solution of 1-*p*-Toluenesulfonyl-1-bromoformaldoxime (0.3 g, 1.0 mmol) in chloroform (10 mL) at room temperature. The resulting solution was stirred for 5 min and water (5 mL) was added. The phases were separated and organic phase dried, filtered and solvent removed *in vacuo* to yield a yellow oil (0.112 g). δ_H: Contains an unidentifiable mixture of products.

Method 6

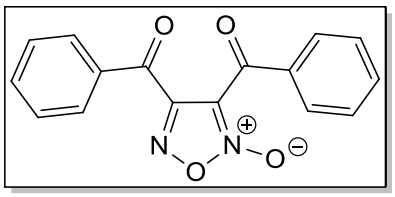
Triethylamine (0.14 mL, 1.00 mmol) was added to a stirring solution of 1-*p*-toluenesulfonyl-1-bromoformaldoxime (0.28 g, 1.01 mmol) in chloroform (10 mL) at room temperature. The resulting solution was stirred for 5 min. Water (5 mL) was added. The phases were separated and organic phase dried, filtered and solvent removed *in vacuo* to yield a pale orange oil (2.9 g). δ_H: Contains mostly **309** with a trace of **307**.

Method 7

Potassium *t*-butoxide (0.1 g, 1.0 mmol) was added to a stirring solution of 1-*p*-toluenesulfonyl-1-bromoformaldoxime (0.3 g, 1.0 mmol) in chloroform (10 mL) at room temperature. The resulting mixture was stirred for 5 min. Water (5 mL) was added and the phases were separated. The organic phase was dried, filtered and solvent removed *in vacuo* to yield a clear oil (0.101 g). δ_H: Contains **299** and a trace of **309**.

5.2 Preparation of furoxans

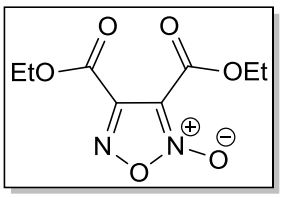
5.2.1 3,4-Dibenzoylfuroxan 314



Triethylamine (0.46 mL, 3.3 mmol) was added to a stirring solution of 1-benzoyl-1-chloroformaldoxime (0.6 g, 3.3 mmol) in ether (20 mL) at room temperature. The resulting cloudy (precipitate formed immediately) pale yellow solution was stirred overnight. The solution was filtered and solvent removed *in*

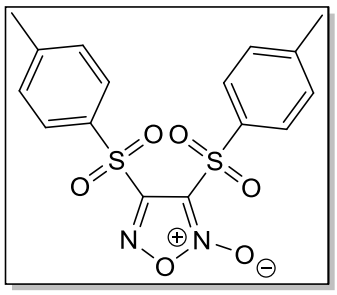
vacuo. Any residual solvent or triethylamine was removed under vacuum to yield the *furoxan* (0.746 g, 78%) as a yellow crystalline solid. m.p. 77.5-80.5 ^{o}C (Lit. 78-80 ^{o}C).[12f] ν_{max} (film): 3066, 3007, 1682, 1614, 1470, 1452, 1329, 1238, 1180, 1035, 923, 846 cm^{-1}; δ_H: 7.55 (4H, m, Ar<u>H</u>), 7.70 (2H, m, Ar<u>H</u>), 7.86 (2H, m, Ar<u>H</u>), 8.20 (2H, m, Ar<u>H</u>); δ_C: 129.1, 129.2, 129.7 and 130.6 (4 x Ar<u>C</u>H), 128.5 and 130.2 (2 x *p*-Ar<u>C</u>H), 135.2 and 135.5 (2 x *i*-Ar<u>C</u>), 154.3 and 170.7 (2 x <u>C</u>=N), 180.4 and 181.8 (2 x <u>C</u>=O). m/z = 295 $[M+H]^+$.

5.2.2 3,4-Diethoxycarbonylfuroxan 315



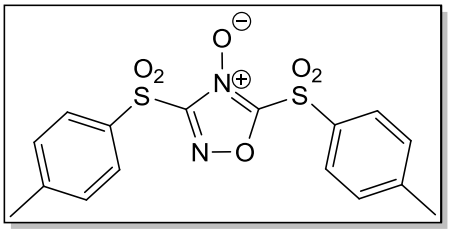
Ethylchloroglyoxalate oxime (0.276 g, 1.82 mmol) and triethylamine (0.200 g, 1.98 mmol) in ether (10 mL) were stirred together for 1 h. The solution was filtered and the solvent was removed *in vacuo*. As evaporation of the solvent did not yield the product, the solid isolated on the filter paper was dissolved in dichloromethane (10 mL) and was washed with water (10 mL). The layers were separated, the organic extract was dried, solvent removed *in vacuo* and compound (0.376 g, 90%) isolated as yellow oil. (Lit. b.p. 115 ^{o}C @1mmHg).[12n] ν_{max} (film): 2987, 2943, 1750, 1626, 1247, 1198, 1024 cm^{-1}; δ_H: 1.42 (6H, m, 2 x C<u>H</u>$_3$), 4.48 (4H, two overlapping q (showing 6 of 8 possible lines), J = 7.15, 7.10, 2 x C<u>H</u>$_2$); δ_C: 8.6 and 13.9 (2 x <u>C</u>H$_3$), 43.8 and 63.6 (2 x <u>C</u>H$_2$), 106.7 and 148.4 (2 x <u>C</u>=N), 155.1 and 156.7 (2 x <u>C</u>=O). HRMS (ESI$^+$) exact mass calculated for $C_8H_{11}N_2O_6$ $[(M+H)^+]$, 231.0617, found 231.0621.

5.2.3 3,4-*bis*-(*p*-Toluenesulfonyl)-furoxan 309



Triethylamine (0.46 mL, 3.3 mmol) was added to a stirring solution of 1-toluenesulfonyl-1-bromoformaldoxime (0.91 g, 3.3 mmol) in ether (20 mL) at room temperature. The resulting orange mixture (precipitate formed immediately) was stirred overnight. The solution was filtered and the filtrate was concentrated *in vacuo* to yield the product (0.37 g, 29%) as a yellow oil. The sample was placed under high vacuum to remove any residual solvent/triethylamine residues and an orange solid was isolated, m.p. 155-158 ^{o}C (Lit. m.p. 183 ^{o}C).[12w] ν_{max} (film): 3067, 2983, 2926, 2185, 1783, 1619, 1594, 1492, 1449, 1376, 1351, 1164, 955 cm^{-1}; δ_H: 2.49 (6H, m, 2 x ArC<u>H</u>$_3$), 7.42 (4H, m, Ar<u>H</u>), 7.80 (2H, m, Ar<u>H</u>), 7.96 (1H, m, Ar<u>H</u>), 8.04 (1H, m, Ar<u>H</u>); δ_C: 21.4, 21.5 and 22.0 (3 x Ar<u>C</u>H$_3$ **309**/**316**), 126.0, 126.5, 129.1, 129.3, 129.7, 130.2, 130.3, 130.5 (8 x Ar<u>C</u>H), 147.5 (<u>C</u>=N). m/z = 198 [M$^+$ of nitrile oxide] furoxan (**309**) not observed in mass spectral analysis.

8 x ArH signals suggest that two products are present. The *p*-substituted aromatic rings should only give 4 signals in the furoxan structure. Therefore the asymmetrical 1,2,4-oxadiazole-4-oxide **316** could be present also. The ^{13}C NMR spectroscopy was taken a long time after synthesis, therefore the nitrile oxide should not be present and would not account for the second set of signals.

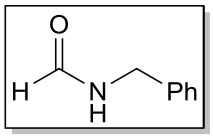


316

6 Reference compounds

6.1 Reference material for amidine degradation

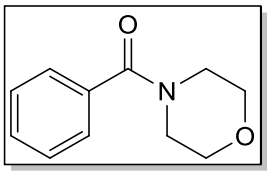
6.1.1 *N*-Benzylformamide 319



Benzylamine (5.54 g, 51.68 mmol) was heated at reflux with ethyl formate (11.50 g, 155.29 mmol) for 24 h. The by-product (ethanol) was evaporated *in vacuo* to yield the amide as clear oil which solidified on standing. Recrystallisation from toluene gave the *formamide* (5.77 g, 83%) as a white solid as a 1:5 mixture of rotamers, m.p. 65 ^{o}C (Lit. m.p. 62-63 ^{o}C).[212] ν_{max} (KBr): 3271, 3056, 3031, 1639, 1534, 1389 cm^{-1}; δ_H: 4.40 (0.33H, d, J = 6.52, CH$_2$ minor), 4.47 (1.61H, d, J = 5.92, CH$_2$ major), 5.96 (1H, bs, NH), 7.32 (5H, m, ArH), 8.17 (0.16H, d, J = 11.94, NHCHO, minor), 8.25 (0.79H, s, NHCHO major); δ_C: 42.2 (CH$_2$ major), 45.6 (CH$_2$ minor), 127.0 (ArCH minor), 127.7 (ArCH major), 127.8 (ArCH major), 128.0 (ArCH minor), 128.8 (ArCH major), 129.0 (ArCH minor), 137.6 (*ipso* C of Ar), 161.0 (CHO major), 164.6 (CHO minor). Ratio minor:major rotamer (1:5). m/z = 271 $[2M+H]^+$, 136 $[M+H]^+$.

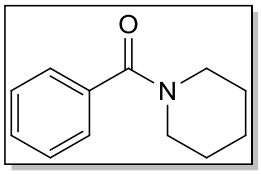
6.2 Reference material for bromo nitrileoxide cycloadditions

6.2.1 *N*-Benzoylmorpholine 322



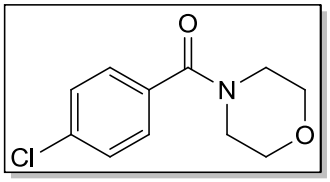
Benzoyl chloride (7.03 g, 0.05 mol) in ether (30 mL) was added dropwise *via* a pressure-equalising addition funnel to a stirring solution of morpholine (4.38 g, 0.05 mol) and triethylamine (5.06 g, 0.05 mol) in the same solvent (50 mL). The resulting white solution was stirred overnight. Ether (~80 mL) was added to the solution as some ether had evaporated off overnight. The solution was filtered and solvent removed *in vacuo* to yield the crude product as a white crystalline solid. The crude product was dissolved in dichloromethane (distilled, ~60 mL) and was washed with water (3 x 40 mL). The dichloromethane extract was dried, filtered and solvent removed *in vacuo* to yield a clear oil. This was diluted in hexane (distilled, ~80 mL) and stored in a freezer for 2 h and left to stand over the weekend. The *amide* (4.03 g, 42%) was isolated as a white crystalline solid, m.p. 67-69 ^{o}C (lit. m.p. 72-74 ^{o}C).[172] ν_{max} (KBr): 3080, 3064, 1626, 1426, 1271, 1254, 1111 cm^{-1}; δ_H: 3.60 [8H, m, N(C$\underline{H}_2$)$_4$O], 7.41 (5H, m, Ar$\underline{H}$); δ_C: 42.5 [N($\underline{C}H_2$)$_2$], 66.9 [O($\underline{C}H_2$)$_2$], 127.1 (*m*-Ar$\underline{C}$H), 128.6 (*o*-Ar$\underline{C}$H), 129.9 (*p*-Ar$\underline{C}$H), 135.3 (*ipso* $\underline{C}$ of Ar), 170.5 ($\underline{C}$=O). m/z = 383 $(2M+H)^+$, 192 $(M+H)^+$.

6.2.2 *N*-Benzoylpiperidine 324



A solution of benzoyl chloride (7.03 g, 0.05 mol) in ether (30 mL) was added dropwise *via* pressure-equalising addition funnel to a stirring solution of piperidine (4.26 g, 0.05 mol) and triethylamine (5.06 g, 0.05 mol) in ether (50 mL). The resulting white cloudy mixture was left to stir overnight. The solution was filtered and solvent removed *in vacuo* to yield the *amide* (6.35 g, 79%) as a yellow oil. (lit m.p. 47-48 ^{o}C).[172] ν_{max} (film): 3058, 1713, 1627, 1577, 1443, 1275 cm^{-1}; δ_H: 1.51 (2H, bs, C$\underline{H}_2$), 1.68 (4H, bs, C$\underline{H}_2$), 3.34 (2H, bs, C$\underline{H}_2$), 3.71 (2H, bs, C$\underline{H}_2$), 7.39 (5H, bs, Ar$\underline{H}$); δ_C: 24.6, 25.6, 26.6, 43.1 and 48.8 (5 x $\underline{C}H_2$ of piperidine ring), 126.8 and 128.4 (2 x Ar$\underline{C}$H), 129.4 (*p*-Ar$\underline{C}$H), 136.5 (*ipso* $\underline{C}$ of Ar), 170.4 ($\underline{C}$=O).

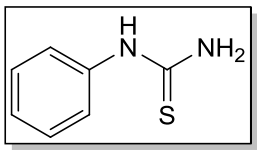
6.2.3 *N*-(*p*-Chlorobenzoyl)-morpholine 327



A solution of *p*-chlorobenzoyl chloride (6.86 g, ~0.04 mol) in ether (50 mL) was added to a stirring solution of triethylamine (5.58 mL, 0.04 mol) and morpholine (3.51 g, 0.04 mmol) in

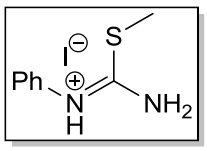
ether (150 mL). A slight exotherm occurred. The resulting white cloudy mixture was stirred over the weekend. Dichloromethane (200 mL) added as the solution had dried out. The solution was washed with water (3 x 200 mL). The combined organic extracts were dried, filtered and the solvent was removed *in vacuo* to yield the *amide* (6.8 g, 77% two steps) as a white solid, m.p. 73-74 ^{o}C (Lit. m.p. 77 ^{o}C).[174] ν_{max} (KBr): 3028, 1626, 1593, 1436, 1112 cm^{-1}; δ_H: 3.69 [8H, bm, N(C<u>H</u>$_2$)$_4$O], 7.40 (4H, m, Ar<u>H</u>); δ_C: 42.8 [N(<u>C</u>H$_2$)], 48.1 [N(<u>C</u>H$_2$)], 66.8 [O(<u>C</u>H$_2$)$_2$], 128.7 and 128.9 (2 x Ar<u>C</u>H), 133.6 (*ipso* <u>C</u> of Ar), 136.0 [*p*-Ar<u>C</u>(Cl)], 169.4 (<u>C</u>=O). m/z = 228 [^{37}Cl M+H]$^+$, 226 [^{35}Cl M+H]$^+$ (100%).

6.2.4 *N*-Phenylthiourea[176] 329



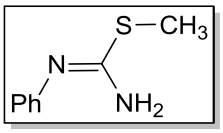
Phenylisothiocyanate (13.82 g, 0.10 mol) was added dropwise *via* Pasteur pipette to a stirring solution of ammonia (6 mL, 0.10 mol) in dichloromethane (300 mL, distilled) at room temperature and the resulting clear solution was stirred at room temperature for 18 h. Water (1000 mL) was added. The solution was transferred to a separating funnel. The phases were separated and the aqueous phase was extracted with distilled dichloromethane (3 x 100 mL). A white emulsion was present. The organic extracts were combined and washed with brine (100 mL). Note: some of the emulsion cleared and distilled dichloromethane (100 mL) was added to clear the remaining emulsion-which disappeared after addition. The combined organic extracts were dried, filtered and the solvent was evaporated *in vacuo* to yield a white crystalline solid. The resulting residue was recrystallised from dichloromethane : hexane (distilled). The *thiourea* (9.65 g, 63%) was isolated by vacuum filtration as a white crystalline solid, m.p. 154-155 ^{o}C (Lit. m.p. 155 ^{o}C). ν_{max} (KBr): 3423, 3276, 1609, 1519, 1444, 1260, 1230 cm^{-1}; δ_H: 6.16 (2H, bs, N<u>H</u>$_2$), 7.24 (2H, m, *o*-Ar<u>H</u>), 7.35 (1H, m, *p*-Ar<u>H</u>), 7.45 (2H, m, *m*-Ar<u>H</u>), 8.18 (1H, bs, N<u>H</u>).

6.2.5 Methyl-*N*-phenylcarbamidothioate hydroiodide[178] 330



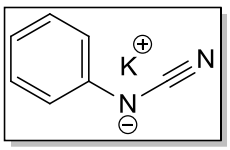
Iodomethane (5 mL, 0.08 mol) was added to a stirring solution of *N*-phenylthiourea (12.18 g, 0.08 mol) in the minimum quantity of acetone and the mixture was stirred overnight at room temperature. The solvent was evaporated *in vacuo* and ether was used to transfer the sample. The sample was then washed with ether. The *product* (22.4 g, 95%) was isolated as a pale cream solid, m.p. 145-145.5 ^{o}C(Lit. m.p. 140 ^{o}C), ν_{max} (KBr): 3079, 1624, 1591, 1569, 1433 cm^{-1}; δ_H: 2.78 (3H, s, SC<u>H</u>$_3$), 7.35 (2H, m, Ar<u>H</u>), 7.44 (3H, m, Ar<u>H</u>).

6.2.6 *N*-Phenyl-*S*-methylisothiourea[178] 331



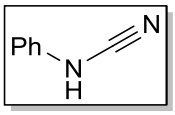
Conc. ammonia (aqueous) solution was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *S*-methyl-*N*-phenylcarbamidothioate hydroiodide (7.51 g, 25.5 mmol) in water (200 mL). *N-Phenyl-S-methylisothiourea* (3.49 g, 82%) precipitated as a white solid which was isolated by vacuum filtration, m.p. 63-65 ^{o}C (Lit. m.p. 72 ^{o}C[177]). ν_{max} (KBr): 3431, 3092, 1619, 1571, 1483, 1275 cm^{-1}; δ_H: 2.46 (3H, s, SC<u>H</u>$_3$), 4.42 (2H, bs, N<u>H</u>$_2$), 6.92 (2H, m, *o*-Ar<u>H</u>), 7.04 (1H, m, *p*-Ar<u>H</u>), 7.31 (2H, m, *m*-Ar<u>H</u>).

6.2.7 Potassium phenylcyanamide[177] 332



A solution of potassium hydroxide (0.66 g, 11.84 mmol) in water (2 mL) was added dropwise *via* Pasteur pipette to a stirring solution of *N*-phenyl-*S*-methylisothiourea (1.96 g, 11.7 mmol) in *iso*-propyl alcohol (6 mL) at room temperature. The resulting clear solution was heated under reflux for ten min. The flask was cooled to room temperature and the solvent was removed *in vacuo* to yield a white solid. The crude product was recrystallised from acetone and left to stand in the fumehood overnight. *Potassium phenylcyanamide* (0.78 g, 42%) was isolated by vacuum filtration as a white solid, m.p. 328 ^{o}C decomp. (Lit. m.p. 345 ^{o}C). ν_{max} (KBr): 3075, 3015, 2077, 1596, 1495, 1323, 1313 cm^{-1}; δ_H(DMSO-d$_6$): 6.32 (1H, tt, J = 1.15, 7.16, *p*-Ar<u>H</u>), 6.58 (2H, m, *o*-Ar<u>H</u>), 6.89 (2H, m, *m*-Ar<u>H</u>); δ_C(DMSO-d$_6$): 113.8 (<u>C</u>≡N), 118.0, 126.1 and 128.3 (3 x Ar<u>C</u>H), 155.4 (*ipso* <u>C</u> of Ar).

6.2.8 Phenylcyanamide[177] 333

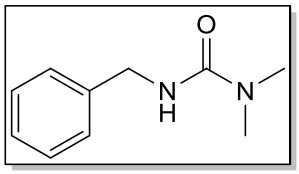


A solution of potassium phenylcyanamide (0.40 g, 2.56 mmol) in *iso*-propyl alcohol (3.75 mL) and water (0.75 mL) was neutralised (to pH 7) with 2 M HCl (aq.) solution. The solvent was evaporated *in vacuo* to yield a pale cream solid. This was dissolved in distilled dichloromethane (30 mL) and was filtered to remove any remaining solids. The solvent was removed *in vacuo* to yield the crude *phenylcyanamide* (0.29 g, 96%) as a pale yellow oil. ν_{max} (film): 3171, 3100, 2987, 2914, 2229, 1601, 1501, 1435, 1302, 1249, 1176 cm^{-1}; δ_H: 5.94 (1H, bs, N<u>H</u>), 7.05 (3H, m, Ar<u>H</u>), 7.33 (2H, m, *m*-Ar<u>H</u>); δ_C: 111.6 (<u>C</u>≡N), 115.4, 123.6 and 129.8 (3 x Ar<u>C</u>H), 137.3 (*ipso* <u>C</u> of Ar). m/z = 237 [2M+H]$^{+}$.

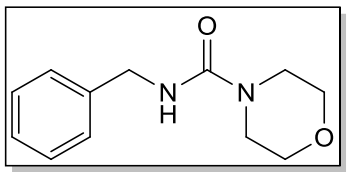
6.3 Decomposition reference products

6.3.1 Ureas

6.3.1.1 1-Benzyl-3-(*N*,*N*-dimethyl)-urea 335



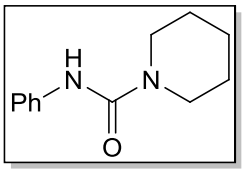
A solution of benzylisocyanate (1 mL, 8.10 mmol) in *dry* toluene (20 mL) was added dropwise *via* a pressure equalising addition funnel to a stirring solution of *N*,*N*-dimethylamine (1.45 mL, 8.12 mmol, 33% in abs ethanol) in *dry* toluene (20 mL) at 70-80 ^{o}C. Following addition, the solution was stirred at 70-80 ^{o}C for 10 min and was then cooled to room temperature. The solvent was removed *in vacuo* to yield a pale yellow oil, which solidified on standing. The sample was recrystallised from methanol to yield the *urea* (1.23 g, 85%) as a white solid, m.p. 64-65 ^{o}C (Lit. m.p. 77 ^{o}C[179]), ν_{max} (KBr) 3312, 3031, 1631, 1536, 1453, 1349, 1234 cm^{-1}; δ_H(DMSO-d$_6$): 2.92 [6H, s, N(C$\underline{H}_3$)$_2$], 4.42 (2H, d, J = 5.55, PhC$\underline{H}_2$), 4.65 (1H, bs, N$\underline{H}$), 7.30 (5H, m, Ar$\underline{H}$); δ_C(DMSO-d$_6$): 36.3 [N($\underline{C}$H$_3$)$_2$], 45.1 (Ph$\underline{C}$H$_2$), 127.3 (*p*-Ar$\underline{C}$H), 127.8 and 128.6 (2 x Ar$\underline{C}$H), 139.7 (*ipso* $\underline{C}$ of Ar); m/z = 179 ([M+H]$^+$, 100%).



6.3.1.2 *N*-Benzylmorpholine-4-carboxamide 336

A solution of benzylisocyanate (1.0 mL, 8.10 mmol) in dry toluene (20 mL) was added dropwise via pressure equalising addition funnel to a stirring solution of morpholine (0.71 mL, 8.12 mmol) in dry toluene (20 mL) at 70-80 ^{o}C. On completion of addition, the solution was stirred at 70-80 °C for 10 min. The solution was cooled and a solid precipitated out of solution which was isolated by vacuum filtration. The urea (1.50 g, 84%) was isolated as a white crystalline solid, m.p. 129-130 °C (Lit. m.p. 123-124 °C).[213] ν_{max} (KBr): 3337, 3076, 3029, 1626, 1543, 1267, 1115 cm^{-1}; δ_H: 3.36 [4H, t, J = 4.92, N(C$\underline{H}_2$)$_2$], 3.68 [4H, t, J = 4.91, O(C$\underline{H}_2$)$_2$], 4.43 (2H, d, J = 5.46, PhC$\underline{H}_2$], 4.73 (1H, bs, N$\underline{H}$), 7.31 (5H, m, Ar$\underline{H}$); δ_C: 44.1 [N($\underline{C}$H$_2$)$_2$], 45.0 (Ph$\underline{C}$H$_2$), 66.5 [O($\underline{C}$H$_2$)$_2$], 127.4 (*p*-Ar$\underline{C}$H), 127.8 and 128.7 (2 x Ar$\underline{C}$H), 139.2 (*ipso* $\underline{C}$ of Ar), 157.7 ($\underline{C}$=O). m/z = 221 ([M+H]$^+$, 100%).

6.3.1.3 *N*-Phenyl-1-piperidine carboxamide 337



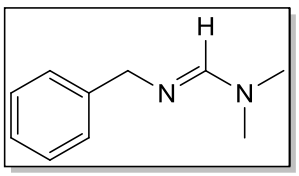
A solution of phenylisocyanate (5.43 mL, 50 mmol) in distilled toluene (50 mL) was added dropwise *via* pressure-equalising addition funnel to a stirring solution of piperidine (4.9 mL, 50 mmol) in distilled toluene (50 mL) at 70-80 ^{o}C. A white solid precipitated from solution. The solution was cooled and the *urea* (9.16 g, 90%) was isolated by vacuum filtration as a white solid, m.p. 166-168 ^{o}C (Lit. m.p. 168.3 ^{o}C).[182] ν_{max} (KBr): 3287, 3054, 1629, 1536, 1449, 1242 cm^{-1}; δ_H: 1.61 [6H, m, (C$\underline{H}_2$)$_3$], 3.42 [4H, m, N(C$\underline{H}_2$)$_2$], 6.47 (1H, bs, N$\underline{H}$), 7.00 (1H, m, *p*-Ar$\underline{H}$), 7.26 (2H, m, *m*-Ar$\underline{H}$), 7.36 (2H, m, *o*-Ar$\underline{H}$); δ_C: 24.4 (CH$_2\underline{C}$H$_2$CH$_2$), 25.7 [N(CH$_2$)$_2$(C$\underline{H}_2$)$_2$], 45.3 [N(C$\underline{H}_2$)$_2$], 119.8, 122.8 and 128.9 (3 x Ar$\underline{C}$H), 139.4 (*ipso* $\underline{C}$ of Ar), 155.0 ($\underline{C}$=O). m/z = 205 (M+H)$^+$, 100%.

7 Preparation of dipolarophiles

7.1 Formamidines

7.1.1 *N,N*-Dimethyl-*N´*-benzylformamidine 339

Method 1



N,N-Dimethylformamide dimethyl acetal (17.0 g, 0.1 mol) was added dropwise *via* a Pasteur pipette to a stirring solution of benzylamine (12.40 g, 0.12 mol) in dry methanol (40 mL). Once addition was complete, the solution was heated under reflux overnight. The reaction mixture was cooled and the solvent was evaporated *in vacuo*. Purification by distillation gave the *amidine* (17.38 g, 93%) as a clear yellow oil, b.p. 132-136 °C @15 mmHg (Lit. b.p. 70-71 ^{o}C @ 0.005 torr).[214] ν_{max} (film): 3084, 3060, 3026, 2911, 1643, 1346, 1106 cm^{-1}; δ_H: 2.88 [6H, s, N(C$\underline{H}_3$)$_2$], 4.45 (2H, s, PhC$\underline{H}_2$), 7.28 (5H, m, Ar$\underline{H}$), 7.38 (1H, s, N=C$\underline{H}$N); δ_C: 37.5 [N($\underline{C}$H$_3$)$_2$], 59.9 (Ph$\underline{C}$H$_2$), 126.2 (*p*-Ar$\underline{C}$H), 127.8 (*o*-Ar$\underline{C}$H), 128.6 (*m*-Ar$\underline{C}$H), 143.7 (*ipso* $\underline{C}$ of Ar), 156.3 (N=$\underline{C}$HN).

Method 2

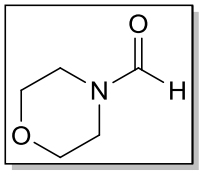
N,N-Dimethylformamide dimethyl acetal (18.6 mL, 140 mmol) in dry methanol (20 mL) was added dropwise *via* pressure-equalising addition funnel to a stirring solution of benzylamine (12.67 mL, 116 mmol) in methanol (20 mL, distilled). The resulting solution was stirred overnight at room temperature and solvent evaporated *in vacuo* to yield a clear

oil. This was purified by kugelröhr distillation, (b.p. 128.5-130.5 ^{o}C @2 mmHg (Lit. b.p. 70-71 ^{o}C @ 0.005 torr)) to give the *amidine* as a clear oil (16.32 g, 87%).[214] ν_{max} (film): 3060, 3026, 2912, 1950, 1650, 1346, 1106 cm^{-1}; δ_H: 2.84 [6H, s, N(C<u>H</u>$_3$)$_2$], 4.43 (2H, s, PhC<u>H</u>$_2$), 7.23 (5H, m, Ar<u>H</u>), 7.35 (1H, s, N=C<u>H</u>N).

Method 3

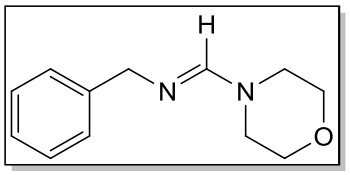
Benzylamine (12.67 mL, 116 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (18.6 mL, 140 mmol) were stirred together at room temperature overnight in chloroform (40 mL). The solvent was evaporated *in vacuo*. The *amidine* was purified by kugelröhr distillation, b.p. 90-110 ^{o}C @ 2 mmHg (Lit. b.p. 70-71 ^{o}C @ 0.005 torr) and isolated as a clear oil (17.32 g, 92%).[214] ν_{max} (film): 3084, 3060, 3026, 2910, 2285, 1656, 1346, 1105 cm^{-1}; δ_H: 2.83 [6H, s, N(C<u>H</u>$_3$)$_2$], 4.44 (2H, s, PhC<u>H</u>$_2$), 7.23 (5H, m, Ar<u>H</u>), 7.34 (1H, s, N=C<u>H</u>N).

7.1.2 *N*-Formylmorpholine 340



98-100% Formic acid (82.96 g, 1.8 mol) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/ice bath), stirring solution of morpholine (156.84 g, 1.8 mol) in toluene (250 mL). On completion of addition, the solution was heated at reflux until 34.5 mL water was collected in a Dean-Stark trap. Solid sodium hydrogen carbonate (6.0 g, 0.1 mol) was added to the cooled solution. This solution was stirred for 30 min, filtered and the solvent was removed *in vacuo*. Purification by vacuum distillation, b.p. 112-114 ^{o}C @25 mmHg (Lit. b.p. 120-122 ^{o}C @ 19-20 mmHg) yielded *N-formylmorpholine* (189.61 g, 91%) as a clear oil.[215] ν_{max} (film): 3103, 1660, 1435, 1399, 1069 cm^{-1}; δ_H: 3.41 [2H, m, N(C<u>H</u>$_{ax}$)$_2$], 3.57 [2H, m, N(C<u>H</u>$_{eq}$)$_2$], 3.68 [4H, m, O(C<u>H</u>$_2$)$_2$], 8.06 (1H, s, C<u>H</u>O).

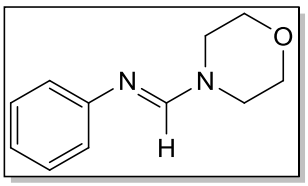
7.1.3 *N*-Benzylformimidoylmorpholine 318



Phosphorous oxychloride (2.76 g, 18 mmol) in benzene (20 mL) was added dropwise to a mechanically stirring solution of *N*-formylmorpholine (1.85 g, 16.1 mmol) in the same solvent (20 mL). The resulting solution was stirred at room temperature for 30 min. A solution of benzylamine (1.7 g, 16.1 mmol) in benzene (20 mL) was then added dropwise to the stirring, biphasic solution over 25 min. The solution was then heated under reflux for 22 h. The stirring reaction mixture was cooled and 6 M NaOH (10 mL) was added. The biphasic solution was transferred to a separating funnel and the

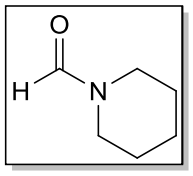
phases were separated. The aqueous layer was washed with ether (2 x 100 mL). The organic extracts were combined, dried and the solvent evaporated *in vacuo* to give pale yellow oil. The oil was purified by kugelröhr distillation (b.p 140-163 ^{o}C @0.8 mmHg) to yield the *amidine* (1.54 g, 47%) as a clear yellow oil. ν_{max} (film): 3060, 3025, 2852, 1650, 1453, 1115 cm^{-1}; δ_H: 3.34 [4H, m, N(C<u>H</u>$_2$)$_2$], 3.68 [4H, m, O(C<u>H</u>$_2$)$_2$], 4.45 (2H, s, PhC<u>H</u>$_2$), 7.30 (6H, m, N=C<u>H</u>N and Ar<u>H</u>); δ_C: 46.1 [N(<u>C</u>H$_2$)$_2$], 59.5 (Ph<u>C</u>H$_2$), 66.7 [O(<u>C</u>H$_2$)$_2$], 126.5, 127.5 and 128.3 (3 x Ar<u>C</u>H), 141.6 (*ipso* <u>C</u> of Ar), 155.0 (N=<u>C</u>HN).

7.1.4 *N*-Phenylformimidoylmorpholine 341



Phosphorous oxychloride (8.97 mL, 98 mmol) in benzene (30 mL) was added dropwise *via* a pressure equalizing addition funnel to a vigorously stirring solution of aniline (7.97 mL, 87 mmol) and *N*-formylmorpholine (9.65 mL, 96 mmol) in benzene (100 mL) at room temperature. The solution was heated under reflux for 4 h. The reaction mixture was cooled, poured onto ice (~100 g) and rendered pH 10-12 (with universal indicator paper) with 6 M NaOH (aq.) solution. The biphasic solution was transferred to a separating funnel and the phases were separated. The aqueous phase was extracted with ether (2 x 100 mL). The combined organic extracts were dried, filtered and solvent removed *in vacuo* to yield the crude amidine as a yellow crystalline solid. Recrystallisation from ether:hexane yielded the *amidine* (8.4 g, 51%) as a pale yellow crystalline solid, m.p. 63-67 ^{o}C(Lit. b.p. 120 ^{o}C @0.05 mmHg) on isolation by vacuum filtration.[102] ν_{max} (KBr): 2965, 1628, 1586, 1169, 1151, 1110 cm^{-1}; δ_H: 3.52 [4H, bs, N(C<u>H</u>$_2$)$_2$], 3.75 [4H, m, O(C<u>H</u>$_2$)$_2$], 6.96 (2H, m, *o*-Ar<u>H</u>), 7.03 (1H, m, *p*-Ar<u>H</u>), 7.27 (2H, m, *m*-Ar<u>H</u>), 7.52 (1H, s, N=C<u>H</u>).

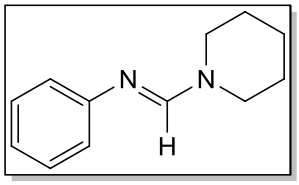
7.1.5 *N*-Formylpiperidine 342



98-100% Formic acid (7.6 mL, 0.2 mol) was added dropwise to a cooled (<10 ^{o}C, water/icebath), stirring solution of piperidine (19.8 mL, 0.2 mol) in toluene (55 mL, distilled). The solution was heated at reflux until a total of 3.6 mL of water was collected (1.5 h) in a Dean-Stark trap. The solution was cooled, solid sodium carbonate (5 g) added and the solution was stirred for 5 min (neutralise excess acid). The solution was filtered and solvent removed *in vacuo* to yield the crude formamide as a pale yellow oil. Vacuum distillation yielded the *amide* (15.88 g, 70%) as a clear oil, b.p. 74-99 ^{o}C @ 25 mmHg (Lit. b.p. 221-222 ^{o}C).[187] ν_{max} (film): 2938, 2858, 1664, 1439, 1399, 1279, 1257, 1210, 1118 cm^{-1}; δ_H: 1.56 [4H, m,

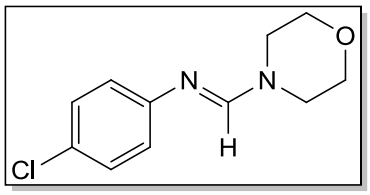
$N(CH_2)_2$-($C\underline{H}_2)_2$], 1.69 [2H, m, $N(CH_2)_2(CH_2)_2C\underline{H}_2$], 3.31 [2H, t, J = 5.6, $N(C\underline{H}_{ax})_2$], 3.48 [2H, t, J = 5.7, $N(C\underline{H}_{eq})_2$], 8.00 (1H, s, C<u>H</u>O).

7.1.6 *N*-Phenylformimidoylpiperidine 343



Phosphorous oxychloride (8.97 mL, 98 mmol) in benzene (30 mL) was added dropwise *via* a pressure-equalising addition funnel to a vigorously stirring solution of aniline (7.93 mL, 87 mmol, freshly distilled just prior to use) and *N*-formylpiperidine (10.66 mL, 96 mmol) in benzene (100 mL). The resulting pale yellow solution was heated under reflux for 4 h. The solution was cooled, poured onto ice (~100 g), brought to pH 10 with 6 M NaOH solution and phases were separated. The aqueous phase was extracted with ether (2 x 100 mL). A cream coloured emulsion formed which was kept with the aqueous phase during extraction with ether. Chloroform (~400 mL) added to aqueous phase containing emulsion and emulsion dissipated. The phases were separated (chloroform and ether extracts were kept separate) and aqueous phase extracted with chloroform (1 x 400 mL). The ether/benzene extracts were dried, filtered and left to stand overnight[38]. The chloroform extracts were combined, dried, filtered and the solvent was removed *in vacuo*. The residue was recrystallised from chloroform:hexane, and the *amidine* was isolated as a pale yellow solid (3.2 g, 19%), m.p. 169-170.5 ^{o}C (Lit. b.p. 134-136 ^{o}C @ 0.5 mmHg).[189] ν_{max} (KBr): 3129, 1690, 1598, 1478, 1341 cm^{-1}; δ_H: 1.69 [6H, m, $(C\underline{H}_2)_3$], 3.83 [2H, m, $N(C\underline{H}_2)$], 4.06 [2H, m, $N(C\underline{H}_2)$], 7.17 (1H, m, *p*-Ar<u>H</u>), 7.28 (2H, m, *m*-Ar<u>H</u>), 7.70 (2H, m, *o*-Ar<u>H</u>), 8.74 (1H, s, N=C<u>H</u>N); δ_C: 23.2, 25.1 and 26.3 [3 x $N(CH_2)(\underline{C}H_2)_3$], 48.2 [$N(\underline{C}H_2)$], 54.0 [$N(\underline{C}H_2)$], 119.7 (*m*-Ar<u>C</u>H), 126.3 (*p*-Ar<u>C</u>H), 129.5 (*o*-Ar<u>C</u>H), 137.3 (*ipso* <u>C</u> of Ar), 150.4 (N=<u>C</u>HN). m/z = 188 [M^+, 100%].

7.1.7 *N*-(*N´-p*-Chlorophenylformimidoyl)-morpholine 345



Phosphorous oxychloride (8.97 mL, 98 mmol) in benzene (30 mL) was added dropwise *via* a pressure-equalising addition funnel to a stirring solution of *p*-chloroaniline (11.11 g, 87 mmol) and *N*-formylmorpholine (9.65 mL, 96 mmol) in benzene (100 mL) at room temperature. The solution was heated under reflux for 4 h. The cooled reaction mixture was poured onto ice (~100 g), stirred overnight and then neutralised with 6 M NaOH and the phases were separated. The aqueous phase was

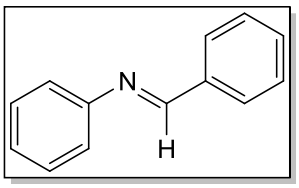
[38] Ether/ benzene extracts contained starting material.

extracted with ether (2 x 100 mL). The organic phases were combined, dried, filtered and solvent evaporated *in vacuo* to yield silver/brown solid. The *amidine* was recrystallised from chloroform:hexane and isolated by vacuum filtration as a grey crystalline solid (12.4 g, 63%), m.p. 66-67 ^{o}C. ν_{max} (KBr): 2965, 2865, 1632, 1582, 1489, 1435, 1357, 1106 cm^{-1}; δ_H: 3.52 [4H, bs, N(C<u>H</u>$_2$)$_2$], 3.74 [4H, m, O(C<u>H</u>$_2$)$_2$], 6.88 (2H, m, *o*-ArC<u>H</u>), 7.21 (2H, m, *m*-ArC<u>H</u>), 7.49 (1H, s, N=C<u>H</u>); δ_C: 45.8 [N(<u>C</u>H$_2$)$_2$], 66.7 [O(<u>C</u>H$_2$)$_2$], 122.2 and 129.1 (2 x Ar<u>C</u>H), 128.0 (*ipso* <u>C</u> of Ar), 150.1 [Ar-<u>C</u>(Cl)], 152.3 (N=<u>C</u>H). m/z = 225 (M$^+$, 100%). HRMS (ESI$^+$) exact mass calculated for $C_{11}H_{13}N_2OCl$ [M+H]$^+$ 225.0795, found 225.785.

7.2 Imines

7.2.1 *N*-Benzylideneaniline 346

Method 1[190]



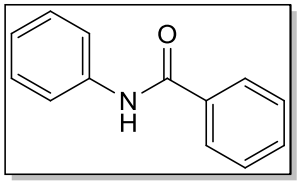
Benzaldehyde (5.31 g, 0.05 mol) in distilled dichloromethane (100 mL) was added dropwise *via* a pressure equalising addition funnel to a stirring solution of aniline (4.66 g, 0.05 mol) in distilled dichloromethane (100 mL). $MgSO_4$ was then added to the stirring solution to remove water as it formed. The solution was stirred for 2.5 h. The resulting dark yellow/orange solution was filtered and the solvent was removed *in vacuo* to yield a pale orange/yellow solid. Recrystallisation from 1:3 ethyl acetate:hexane afforded the *imine* (7.98 g, 89%) as a pale yellow solid, m.p. 49-50.5 ^{o}C (Lit. 51 ^{o}C). ν_{max} (KBr): 3059, 1626, 1589, 1493, 748, 698 cm^{-1}; δ_H: 7.22 (3H, m, Ar<u>H</u>), 7.39 (2H, m, Ar<u>H</u>), 7.48 (3H, m, Ar<u>H</u>), 7.90 (2H, m, Ar<u>H</u>), 8.46 (1H, s, N=C<u>H</u>N).

Method 2[113,216]

Benzaldehyde (31.84 g, 0.3 mol) was added to neat aniline (27.94 g, 0.3 mol). Toluene (200 mL) was added and the solution was stirred and Dean Stark trap was fitted. The solution was heated at reflux until 5.3 mL water was collected (3 h). Solvent evaporated *in vacuo* to yield *imine* (53.62 g, 99%) as a brown solid, m.p. 48-51 ^{o}C (Lit. 50-51 ^{o}C). δ_H: 7.22 (3H, m, Ar<u>H</u>), 7.39 (2H, m, Ar<u>H</u>), 7.48 (3H, m, Ar<u>H</u>), 7.90 (2H, m, Ar<u>H</u>), 8.46 (1H, s, N=C<u>H</u>N); δ_C: 120.9, 125.9, 128.8, 128.8, 129.2 and 131.4 (6 x Ar<u>C</u>H), 136.3 (*ipso* <u>C</u> of Ar), 152.1 (*ipso* <u>C</u> of Ar), 160.4 (N=<u>C</u>H).

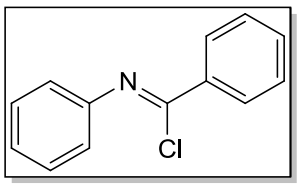
7.3 Benzamidines

7.3.1 *N*-Benzoylaniline 347



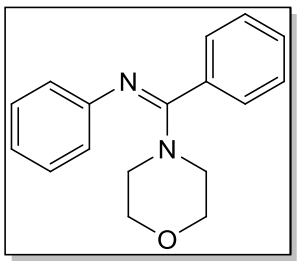
Benzoylchloride (19.7 g, 0.1 mol) in THF (25 mL, distilled) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/ice bath), stirring solution of aniline (13.0 g, 0.1 mol) and pyridine (75 mL) in THF (25 mL, distilled). The reaction was stirred overnight. The resulting solution was poured carefully onto 6 M HCl (1L). The resulting solid was isolated by vacuum filtration and washed with water (4 x 300 mL). The resulting grey solid was recrystallised from 96% ethanol and left to stand overnight. The *amide* (23.6 g, 85%) was isolated by vacuum filtration as a grey crystalline solid, m.p. 166-168 ^{o}C (Lit. m.p. 165-167 ^{o}C).[217] ν_{max} (KBr): 3343, 3051, 1655, 1599, 1529, 1437, 1321 cm^{-1}; δ_H: 7.16 (1H, m, ArH), 7.38 (2H, m, ArH), 7.52 (3H, m, ArH), 7.66 (2H, m, ArH), 7.79 (1H, bs, NH), 7.87 (2H, m, ArH); δ_C: 120.2, 124.6, 127.0, 128.9, 129.2, 131.9 (6 x ArCH), 135.0 (*ipso* C of Ar), 137.9 (*ipso* C of Ar), 165.7 (C=O).

7.3.2 *N*-Phenylbenzimidoyl chloride[218] 348



N-Benzoylaniline (10.79 g, 0.055 mol) and phosphorous pentachloride (10.45 g, 0.050 mol) were heated under reflux in toluene (150 mL) for 17 h. The reaction mixture was then cooled to room temperature and solvent removed *in vacuo*. Benzene (2 x 20 mL) was added (to remove $POCl_3$) and evaporated each time. The remaining residue was heated to ~60 ^{o}C on rotary evaporator for 1 h to remove any residual $POCl_3$. The crude imidoyl chloride was used directly in the next step.

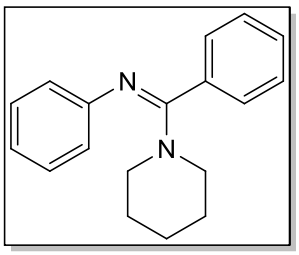
7.3.3 *N*-(*N´*-Phenylbenzimidoyl)-morpholine 349



Morpholine (8.71 g, 0.1 mol) in ether (50 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of crude *N*-phenylbenzimidoyl chloride (~0.05 mol) in ether (100 mL). The reaction mixture was then stirred overnight at room temperature (21 h). The solvent was removed *in vacuo* and the resulting residue was acidified with 6 M HCl (aq) (100 mL). The solid was isolated by vacuum filtration and the filtrate was basified with 6 M NaOH (aq.) solution. The solution became lighter in colour and cloudier as the base was added. At pH 14, the solution was completely cloudy and pale yellow in

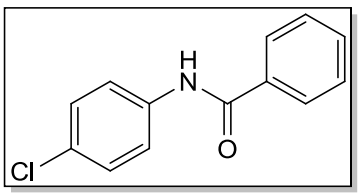
colour. This solution was then extracted with ether (3 x 70 mL). The organic phases were combined, dried, filtered and solvent removed *in vacuo* to yield a pale yellow residue. Recrystallisation from hexane gave the *amidine* (7.1 g, 53% over two steps) as pale orange crystalline solid, m.p. 92-93 ^{o}C (Lit. m.p. 88 ^{o}C).[192] ν_{max} (film): 3046, 3024, 1613, 1590, 1372, 1278, 1129 cm^{-1}; δ_H: 3.41 [4H, bs, N(C$\underline{H}_2$)$_2$], 3.75 [4H, m, O(C$\underline{H}_2$)$_2$], 6.56 (2H, m, Ar$\underline{H}$), 6.75 (1H, m, *p*-Ar$\underline{H}$), 7.00 (2H, m, Ar$\underline{H}$), 7.11 (2H, m, Ar$\underline{H}$), 7.23 (3H, m, Ar$\underline{H}$); δ_C: 46.7 [N(C$\underline{H}_2$)$_2$], 66.8 [O(C$\underline{H}_2$)$_2$], 121.3, 122.7, 128.2, 128.3, 128.8 and 129.1 (6 x Ar$\underline{C}$H), 133.1 (*ipso* $\underline{C}$ of Ar), 150.8 (*ipso* $\underline{C}$ of Ar), 160.7 (N=$\underline{C}$). m/z = 267 ([M+H]$^+$, 100%).

7.3.4 *N*-(*N´*-Phenylbenzimidoyl)-piperidine 350



Piperidine (7.4 mL, 75 mmol) in ether (50 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of crude *N*-phenylbenzimidoyl chloride (~0.05 mol) in ether (100 mL) and the resulting solution was stirred overnight at room temperature. The bright orange/red solution was acidified with 6 M HCl (aq) (100 mL). The solution was filtered by gravity filtration and the filtrate was basified with aqueous 6 M sodium hydroxide solution to pH 8 when the solution became cloudy and pale cream in colour. The solution was extracted with ether (3 x 70 mL). The organic extracts were combined, dried, filtered and solvent evaporated *in vacuo*. The *amidine* (7.58 g, 57%, over two steps) was isolated as yellow oil. (Lit. m.p. 51 ^{o}C).[192] ν_{max} (film): 3074, 3056, 1589, 1272, 1249, 1109 cm^{-1}; δ_H: 1.64 [6H, m, (C$\underline{H}_2$)$_3$], 3.37 [4H, bs, N(C$\underline{H}_2$)$_2$], 6.54 (2H, m, Ar$\underline{H}$), 6.69 (1H, m, *p*-Ar$\underline{H}$), 6.97 (2H, m, Ar$\underline{H}$), 7.09 (2H, m, Ar$\underline{H}$), 7.18 (3H, m, Ar$\underline{H}$); δ_C: 24.9 and 25.9 (2 x $\underline{C}$H$_2$), 47.0 [N($\underline{C}$H$_2$)$_2$], 120.7, 122.9, 126.8, 128.0, 128.3 and 129.0 (6 x Ar$\underline{C}$H), 134.1 (*ipso* $\underline{C}$ of Ar), 151.4 (*ipso* $\underline{C}$ of Ar), 160.7 (N=$\underline{C}$). m/z = 265 [M+H]$^+$.

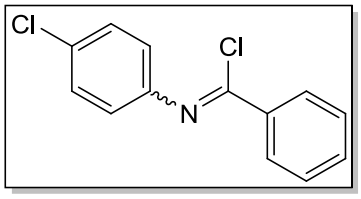
7.3.5 *N*-Benzoyl-*p*-chloroaniline 351



Benzoyl chloride (19.69 g, 0.14 mol) in dry THF (25 mL) was added dropwise to a cooled (<10 ^{o}C, water/ice bath), stirring solution of *p*-chloroaniline (17.86 g, 0.14 mol) and pyridine (75 mL) in dry THF (25 mL). The resulting dark grey solution was stirred overnight (17.25 h) and was poured slowly onto 6 M HCl (1 L). The solid precipitate was isolated by vacuum filtration and washed with water (3 x 400 mL). The resulting dark grey solid was recrystallised from 96% ethanol and left to stand for 6 h. The *amide* (26.43 g, 82%) was isolated by vacuum filtration as a grey crystalline

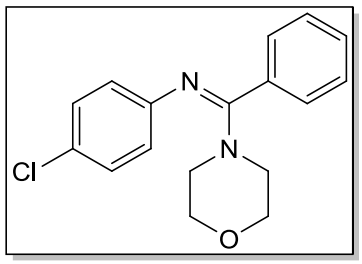
solid, m.p. 190-191.5 °C (Lit. m.p. 188-190 °C).[194] ν_{max} (KBr): 3349, 1654, 1595, 1518, 1493, 718 cm^{-1}; δ_H: 7.35 (2H, m, ArH), 7.51 (3H, m, ArH), 7.60 (2H, m, ArH), 7.80 (1H, bs, NH), 7.86 (2H, m, ArH); δ_C: 121.4, 127.0, 128.9, 129.2 and 132.1 (5 x ArCH), 129.6 (*ipso* C of Ar), 134.6 [ArC(Cl)], 136.5 (*ipso* C of Ar), 165.7 (C=O). HRMS (ESI^+) exact mass calculated for $C_{13}H_{10}NOCl$ [$(M+H)^+$], 232.0529, found 232.0520.

7.3.6 *N*-*p*-Chlorophenylbenzimidoyl chloride[218] 352



A mixture of *N*-benzoyl-(*p*-chloroaniline) (12.51 g, 0.05 mol) and phosphorous pentachloride (10.42 g, 0.05 mmol) was heated under reflux in toluene (150 mL) for 17.5 h. A $CaCl_2$ guard tube was fitted to the condenser. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. Benzene (2 x 20 mL) was added twice and evaporated each time (to remove excess $POCl_3$). The remaining residue was heated to ~60 °C on rovac to remove any residual $POCl_3$. The crude imidoyl chloride was used directly in the step.

7.3.7 *N*-(*p*-Chlorophenyl)-benzimidoylmorpholine 353

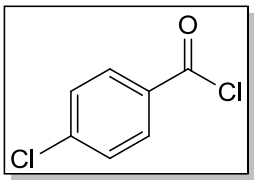


Morpholine (8.72 g, 0.1 mol) in ether (50 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 °C, water/icebath), stirring solution of the crude *N*-*p*-chlorophenylbenzimidoyl chloride (~0.05 mol) in ether (100 mL). The resulting solution was stirred overnight at room temperature. The solvent was removed *in vacuo* and the resulting residue was acidified with 6 M HCl (100 mL). The solid was collected by filtration and the filtrate was basified with 6 M aqueous sodium hydroxide solution to pH 14. At this point, the solution was cream coloured and cloudy with some brown solid. The solution was left to stand overnight. The solution was transferred to a separating funnel and extracted with ether (3 x 70 mL). The organic phases were combined, dried, filtered and solvent evaporated *in vacuo*. The resulting residue was recrystallised from hexane and the *amidine* (7.33 g, 49% over two steps) isolated by vacuum filtration as a pale orange/yellow crystalline solid, m.p. 98-99 °C (Lit. m.p. 113.5 °C).[192] ν_{max} (film): 3047, 2853, 1627, 1597, 1394, 1252, 1111, 770 cm^{-1}; δ_H: 3.41 [4H, bs, $N(CH_2)_2$], 3.74 [4H, bs, $O(CH_2)_2$], 6.47 (2H, m, ArH of *p*-substituted Ar), 6.96 (2H, m, ArH of *p*-substituted Ar), 7.09 (2H, m, ArH), 7.26 (3H, m, ArH); $\delta_{C(500MHz)}$: 46.6 [$N(CH_2)_2$], 66.8 [$O(CH_2)_2$], 123.9, 128.2, 128.5, 129.0 and 129.0 (5

x ArCH), 126.4 (*ipso* C of Ar), 132.7 (*ipso* C of Ar), 149.5 [ArC(Cl)], 161.0 (N=C). m/z = 303 [$(M+H)^+$ ^{37}Cl], 301 ([$M+H]^+$ ^{35}Cl, 100%).

7.3.8 *p*-Chlorobenzoyl chloride 354

Method 1



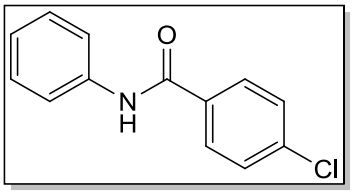
Neat thionyl chloride (11.61 mL, 0.16 mol) was added to a stirring solution of *p*-chlorobenzoic acid (6.27 g, 0.04 mol) in dichloromethane (35 mL, distilled) and the resulting solution was heated at reflux for 8.5 h. IR (1776 cm^{-1}) confirmed formation of the acid chloride. Solvent removed *in vacuo* to yield the crude *acid chloride* (6.86 g, 98%) as a pale yellow solid which was used immediately without further purification.

Method 2

Oxalyl chloride (3.5 mL, 0.04 mol) was added dropwise *via* pressure-equalising addition funnel to a stirring suspension of 4-chlorobenzoic acid (6.27 g, 0.04 mol) in dichloromethane (50 mL) and the resulting solution was stirred at room temperature for 69 h. IR (NaCl) confirmed acid chloride peak (1776 cm^{-1}). Solvent removed *in vacuo* and crude product (~0.04 mol) used directly in next step.

IR of the C=O of the acid shifted from 1677 cm^{-1} to 1662 cm^{-1} indicating conversion to the acid chloride.

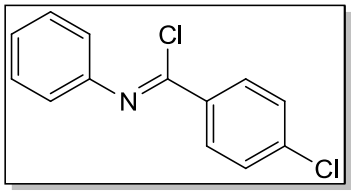
7.3.9 *N*-(*p*-Chlorobenzoyl)-aniline 355



p-Chlorobenzoyl chloride (~0.04 mol) in dry THF (25 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of pyridine (75 mL) and aniline (3.8 mL, 0.04 mol) in dry THF (25 mL). The reaction mixture was stirred overnight and poured slowly onto 6 M HCl (1 L). A pale orange solid precipitated which was collected by vacuum filtration and was washed thoroughly with water. Recrystallisation from 95% ethanol yielded the *amide* (7.14 g, 77%) as a white crystalline solid, m.p. 198-199 ^oC (Lit. m.p. 199-200 ^oC).[195] ν_{max} (film): 3351, 1653, 1598, 1529, 1439, 753 cm^{-1}; δ_H: 7.17 (1H, m, *p*-ArH), 7.38 (2H, t, J = 8.0, *m*-ArH), 7.47 (2H, m, *m*-ArH), 7.62 (2H, m, *o*-ArH), 7.75 (1H, bs, NH), 7.82 (2H, m, *o*-ArH of *p*-ClAr); δ_C: 120.2 (*o*-ArCH of ArN), 124.8 (*p*-ArCH of ArN), 128.5 (*m*-ArCH of

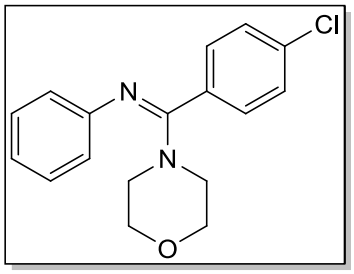
p-Cl-Ar), 129.1 (*o*-ArCH of *p*-Cl-Ar), 129.2 (*m*-ArCH of ArN), 133.3 [ArC(Cl)], 137.6 (*ipso* C of *p*-Cl-Ar), 138.2 (*ipso* C of ArN), 164.6 (C=O).

7.3.10 *N*-Phenyl-(*p*-chlorobenzimidoyl) chloride[218] 356



N-(*p*-Chlorobenzoyl)-aniline (6.95 g, 0.03 mol) and phosphorous pentachloride (6.34 g, 0.03 mol) were heated under reflux in toluene (90 mL) overnight. The solvent was removed *in vacuo* at 60 ^{o}C for 2 h to ensure removal of excess $POCl_3$. IR shows the formation of the *imidoyl chloride* peak *(1654 cm^{-1})*. The crude reaction mixture *(*7.4 g, 98%*)* was used directly in next step.

7.3.11 *N*-Phenyl-(*p*-chlorobenzimidoyl)-morpholine 357



Morpholine (5.24 g, 0.06 mol) in ether (30 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-phenyl-(*p*-chlorobenzimidoyl) chloride (~ 30 mmol) in ether (90 mL) and the resulting solution was stirred overnight at room temperature. The solvent was removed under vacuum and the remaining residue was acidified with 6 M HCl solution (60 mL). The solid which formed was collected by vacuum filtration and the filtrate was basified with 6 M NaOH. The product was extracted with ether (1 x 50 mL) and dichloromethane (2 x 75 mL, distilled). The organic extracts were combined, dried and the solvent evaporated *in vacuo*. A pale yellow solid was isolated. Recrystallisation from hexane afforded the pure *amidine* (4.74 g, 52% (2 steps)) as a pale yellow crystalline solid (m.p. 138-140 ^{o}C) which was isolated by vacuum filtration. ν_{max} (film): 3071, 3011, 1587, 1485, 1417, 742 cm^{-1}; δ_H: 3.38 [4H, bs, N(C$\underline{H}_2$)$_2$], 3.74 [4H, m, O(C$\underline{H}_2$)$_2$], 6.53 (2H, m, Ar$\underline{H}$), 6.78 (1H, m, *p*-Ar$\underline{H}$), 7.03 (4H, m, Ar$\underline{H}$), 7.21 (2H, m, Ar$\underline{H}$); δ_C: 46.7 [N($\underline{C}$H$_2$)$_2$], 66.8 [O($\underline{C}$H$_2$)$_2$], 121.5, 122.5, 128.4, 128.7 and 130.5 (5 x Ar$\underline{C}$H), 131.4 [*ipso* $\underline{C}$ of Ar], 134.8 [*ipso* $\underline{C}$ of Ar], 150.4 [Ar$\underline{C}$(Cl)], 159.5 (N=$\underline{C}$). m/z = 303 [(M+H)$^{+}$ ^{37}Cl], 301 [(M+H)$^{+}$ ^{35}Cl, 100%]; HRMS (ESI^{+}) exact mass calculated for $C_{17}H_{18}N_2OCl$ [M+H]$^{+}$ 301.1108, found 301.1102.

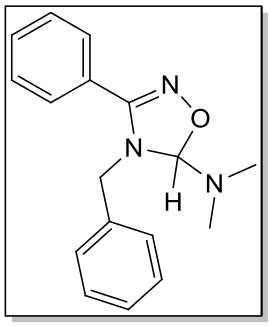
8 Preparation of Δ²-1,2,4-oxadiazolines

8.1 1,3-Dipolar cycloaddition reactions with formamidines

8.1.1 Reactions with *N*,*N*-dimethyl-*N*´-benzylformamidine

8.1.1.1 Attempted preparation of 3-phenyl-4-benzyl-5-(*N*´,*N*´-dimethyl)-Δ²,1,2,4-oxadiazoline 366 with the formation of decomposition products benzonitrile 175 and 1-benzyl-3-(*N*,*N*-dimethyl)-urea 335

Method 1



Benzohydroximoyl chloride (0.162 g, 1.04 mmol) in ether (10 mL) was added dropwise to a cooled (<10 °C, water/icebath) stirring solution of *N*,*N*-dimethyl-*N*´-benzylformamidine (0.165 g, 1.01 mmol) and triethylamine (0.1 g, 1.1 mmol) in ether (10 mL) over 5 min. The white cloudy mixture was warmed to room temperature and allowed to stir overnight. Water (10 mL) was added to the stirring solution, the precipitate dissolved immediately on addition to yield a clear biphasic solution. The solution was transferred to a separating funnel and the phases were separated. The aqueous layer was washed with ether (1 x 10 mL) and separated. The organic extracts were combined, dried, filtered and the solvent was removed *in vacuo*. The sample was then placed under high vacuum to remove any residual solvent and isolated as a white solid. The product was a mixture of benzonitrile (**175**) and 1-benzyl-3-(*N*,*N*-dimethyl)-urea (**335**) in a 1 : 1 ratio. δ_H: 2.91 [6H, s, N(C<u>H</u>$_2$)$_2$ **335**], 4.41 (2H, d, J = 5.6, PhC<u>H</u>$_2$ **335**), 4.80 (1H, bs, NH **335**), 7.32 (4H, m, Ar<u>H</u> **335** & **175**), 7.47 (2H, m, Ar<u>H</u> **335** & **175**), 7.63 (4H, m, Ar<u>H</u> **335** & **175**); δ_C: 36.3 [N(<u>C</u>H$_3$)$_2$ **335**], 45.0 (Ph<u>C</u>H$_2$ **335**), 112.4 (*ipso* <u>C</u> of Ar **175**), 118.9 (<u>C</u>≡N **175**) 127.2, 127.7, 128.6, 129.2, 132.2 and 132.8 (6 x Ar<u>C</u>H **335** & **175**), 139.8 (*ipso* <u>C</u> of Ar **335**), 158.4 (<u>C</u>=O **335**).

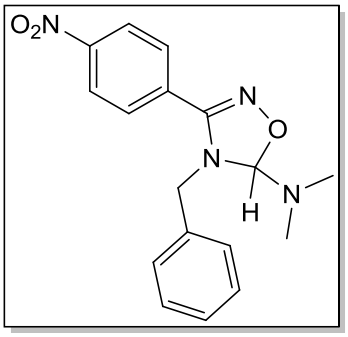
Method 2

Benzohydroximoyl chloride (1.03 g, 6.6 mmol) in ether (20 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 °C, water/icebath) stirring solution of *N*,*N*-dimethyl-*N*´-benzylformamidine (1.055 g, 6.5 mmol) and triethylamine (0.658 g, 6.5 mmol) in ether (35 mL). Ether (10 mL) was added *via* the addition funnel to rinse the funnel and apparatus clear of any solid residue. The resulting white cloudy mixture was

warmed to room temperature and stirred for 1 h. The solution was then filtered to remove the solid precipitate and the solvent was evaporated *in vacuo* (without heat) to yield the crude *oxadiazoline* (0.92 g, 50%) as a pale orange liquid. The sample was placed under high vacuum to remove any residual solvent. However, the oxadiazoline had decomposed during this time.

8.1.1.2 3-(*p*-Nitrophenyl)-4-benzyl-5-(*N´*,*N´*-dimethyl)-Δ²,1,2,4-oxadiazoline 367

Method 1



A solution of *p*-nitrobenzohydroximoyl chloride (0.840 g, 4.19 mmol) in distilled dichloromethane (15 mL) was added dropwise to a cooled (<10 °C, water/icebath), stirring solution of *N´*-benzyl-*N*,*N*-dimethylformamidine (0.686 g, 4.23 mmol) and triethylamine (0.428 g, 4.22 mmol) in dichloromethane (20 mL) over 20 min. The resulting bright orange solution was stirred at room temperature for ten minutes. Water (30 mL) added to dissolve the precipitate and the solution was stirred. The phases were separated and the aqueous phase was extracted with dichloromethane (20 mL). The organic phases were combined, dried, filtered and solvent removed *in vacuo* (without heat) to yield the crude *oxadiazoline* (2.42 g, >100%[39]) as a brown oil. ν_{max} (film): 3055, 2955, 1706, 1525, 1348 cm^{-1}; δ_H: 2.41 [1H, s, N(C<u>H</u>$_3$)$_2$ **367**], 2.89 [6H, s, N(C<u>H</u>$_3$)$_2$ **339**], 4.40 (0.5H, m, PhC<u>H</u>$_2$ **367**), 4.44 (2H, s, PhC<u>H</u>$_2$ **339**), 6.14 (0.13H, s, NC<u>H</u>ON **367**), 6.76 (0.83H, s), 7.29 (5.45H, m, Ar<u>H</u> **367**), 7.39 (1H, s, N=C<u>H</u> **339**), 7.76 (2H, m, *o*-Ar<u>H</u>), 8.28 (2H, m, *m*-Ar<u>H</u>). Ratio of *N´*-benzyl-*N*,*N*-dimethylformamidine (**339**) : oxadiazoline (**367**) was 1 : 0.13.

Method 2

p-Nitrobenzohydroximoyl chloride (1.306 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 °C, water/icebath) stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.055 g, 6.50 mmol) and triethylamine (0.66 g, 6.51 mmol) in ether (35 mL). The yellow cloudy mixture which resulted was warmed to room temperature and stirred for 1 h. The solution was filtered to remove the insoluble solid. The solvent was evaporated *in vacuo* (without heat) to yield the

[39] ^{1}H NMR spectrum shows dichloromethane is present in the sample.

crude *oxadiazoline* (0.4 g, 19%) as a bright yellow solid, m.p. 78-80 ^{o}C. The sample was placed under high vacuum for 20 min to remove any residual solvent. ν_{max} (KBr): 3082, 3063, 1568, 1520, 1441, 1354 cm^{-1}; δ_H: 2.41 [6H, s, N(C<u>H</u>$_3$)$_2$], 4.40 (2H, q, J = 16.0, PhC<u>H</u>$_2$), 6.14 (1H, s, NC<u>H</u>ON), 7.15 (2H, m, Ar<u>H</u>), 7.33 (3H, m, Ar<u>H</u>), 7.75 (2H, m, *o*-Ar<u>H</u> of *p*-NO$_2$-Ar), 8.28 (2H, m, *m*-Ar<u>H</u> of *p*-NO$_2$-Ar); δ_C: 36.7 [N(<u>C</u>H$_3$)$_2$], 48.3 (Ph<u>C</u>H$_2$), 107.7 [N<u>C</u>HON], 124.1, 127.1, 128.0, 129.0 and 129.1 (5 x Ar<u>C</u>H), 132.0 and 136.2 (2 x *ipso* <u>C</u> of Ar), 149.0 (*p*-NO$_2$-<u>C</u>Ar), 154.8 (<u>C</u>=N). m/z = 179 ([M+H]$^+$, 1-benzyl-3-(*N*,*N*-dimethyl)-urea (**335**)), 149 ([M+H]$^+$ *p*-nitrobenzonitrile (**378**)).

Method 3

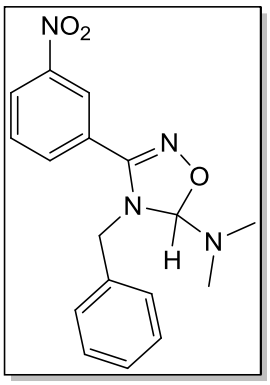
p-Nitrobenzohydroximoyl chloride (1.31 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.06 g, 6.54 mmol) and triethylamine (0.66 g, 6.51 mmol) in ether (35 mL). The bright yellow/orange cloudy mixture which resulted was warmed to room temperature and stirred for 10 min. The solution was filtered to give a bright yellow clear solution. The solvent was evaporated *in vacuo* to yield the crude *oxadiazoline* (1.02 g, 47%) as a yellow solid. ν_{max} (film): 3107, 3031, 1634, 1531, 1349 cm^{-1}; δ_H: 2.41 [6H, s, N(C<u>H</u>$_3$)$_2$], 4.41 (2H, q, J = 16.1, PhC<u>H</u>$_2$), 6.14 (1H, s, NC<u>H</u>ON), 7.16 (2H, m, Ar<u>H</u>), 7.30 (3H, m, Ar<u>H</u>), 7.75 (2H, m, *o*-Ar<u>H</u> of *p*-NO$_2$Ar), 8.28 (2H, m, *m*-Ar<u>H</u> of *p*-NO$_2$Ar). The method of producing the oxadiazoline is reproducible from method 2 to method 3.

Method 4 NMR spectroscopy tube reaction

Triethylamine (1 mL, 0.07 M solution in $CDCl_3$) was added directly to *p*-nitrobenzohydroximoyl chloride (14.10 mg, 0.07 mmol) and the solution was mixed briskly. A 0.6 mL quantity of solution was transferred to an NMR spectroscopy tube and a ^{1}H NMR spectrum was run immediately. Once the NMR spectroscopic analysis was complete, the NMR spectroscopy tube contents were returned to the sample vial and were combined with neat *N*,*N*-dimethyl-*N´*-benzylformamidine (11.70 mg, 0.072 mmol). This solution was mixed briskly and 0.6 mL of this solution was placed in an NMR spectroscopy tube and sample submitted for ^{1}H NMR spectroscopic analysis. Proton NMR spectra taken at intervals over a period of 27.5 h showed that the oxadiazoline had formed immediately and then converted into a mixture of the *p*-nitrobenzonitrile (**378**) and 1-benzyl-3-(*N*,*N*-dimethyl)-urea (**335**)

8.1.1.3 3-(*m*-Nitrophenyl)-4-benzyl-5-(*N´,N´*-dimethyl)-Δ²,1,2,4-oxadiazoline 368

Method 1



A solution of *m*-nitrobenzohydroximoyl chloride (0.849 g, 4.2 mmol) in distilled dichloromethane (15 mL) was added dropwise to a stirring, cooled (<10 °C, ice/water bath) solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (0.699 g, 4.3 mmol) and triethylamine (0.439 g, 4.3 mmol), also in distilled dichloromethane (20 mL), over ten minutes. The solution was stirred (<10 °C, water/icebath) for ten minutes further, then warmed to room temperature and stirred for ten minutes. Water (30 mL) was added to dissolve the precipitate and the resulting biphasic solution was stirred. The phases were separated and the aqueous phase was extracted with dichloromethane (15 mL). The combined organic extracts were dried, filtered and solvent evaporated *in vacuo* to give the crude *oxadiazoline* with residual solvent (2.04 g, >100%[40]) as a yellow viscous liquid. ν_{max} (film): 3088, 3050, 2875, 1635, 1534, 1355 cm^{-1}; δ_H: 2.42 [6H, s, N(C<u>H</u>$_3$)$_2$], 4.42 (2H, q, J = 16.6, PhC<u>H</u>$_2$), 6.14 (1H, s, NC<u>H</u>ON), 7.15 (2H, m, Ar<u>H</u>), 7.33 (3H, m, Ar<u>H</u>), 7.63 (1H, t, J = 8.0, *m*-Ar<u>H</u> of *m*-NO_2-Ar), 7.90 (1H, m, *o*-Ar<u>H</u> of *m*-NO_2-Ar), 8.32 (1H, m, *p*-Ar<u>H</u> of *m*-NO_2-Ar), 8.43 (1H, m, *o*-Ar<u>H</u> of *m*-NO_2-Ar); δ_C: 36.9 [N(<u>C</u>H$_3$)$_2$], 48.2 (Ph<u>C</u>H$_2$), 107.4 (N<u>C</u>HON), 123.1, 125.2, 127.1, 128.0, 129.0, 130.2 and 134.0 (7 x Ar<u>C</u>H), 127.5 (*ipso* <u>C</u> of Ar), 136.1 (*ipso* <u>C</u> of Ar), 148.4 (Ar<u>C</u>-NO_2), 154.6 (<u>C</u>=N).

Method 2

m-Nitrobenzohydroximoyl chloride (1.31 g, 6.52 mmol) in ether (20 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 °C, water/icebath), stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.06 g, 6.51 mmol) and triethylamine (0.66 g, 6.57 mmol) in ether (35 mL). The cloudy pale yellow solution which resulted was warmed to room temperature and stirred for 1 h. The precipitate was removed by filtration and the solvent removed *in vacuo* without heat to yield the crude oxadiazoline as a pale yellow solid. The sample was placed under high vacuum to remove residual solvent and the *oxadiazoline* (0.478 g, 23%) was isolated as a yellow solid, m.p. 69-80 °C. ν_{max} (film): 3107, 3082, 3062, 1591, 1535, 1527, 1347 cm^{-1}; δ_H: 2.42 [6H, s, N(C<u>H</u>$_3$)$_2$],

[40]Dichloromethane present in product.

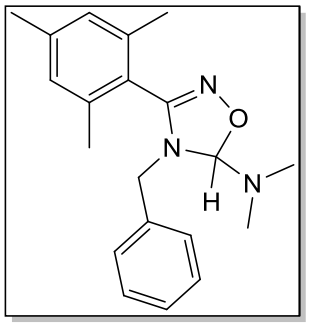
4.41 (2H, q, J = 15.9, PhC$\underline{H}_2$), 6.14 (1H, s, NC$\underline{H}$ON), 7.15 (2H, m, Ar$\underline{H}$), 7.33 (3H, m, Ar$\underline{H}$), 7.62 (1H, t, J = 8.0, *m*-Ar$\underline{H}$ of *m*-NO_2-Ar), 7.89 (1H, m, *o*-Ar$\underline{H}$ of *m*-NO_2-Ar), 8.31 (1H, m, *p*-Ar$\underline{H}$ of *m*-NO_2-Ar), 8.42 (1H, m, *o*-Ar$\underline{H}$ of *m*-NO_2-Ar); δ_C: 36.7 [N($\underline{C}H_3)_2$], 48.2 (Ph$\underline{C}H_2$), 107.5 (N$\underline{C}$HON), 123.1, 125.2, 127.2, 128.0, 129.0, 130.1 and 134.0 (7 x Ar$\underline{C}$H), 127.5 (*ipso* $\underline{C}$ of Ar), 136.1 (*ipso* $\underline{C}$ of Ar), 148.4 (Ar$\underline{C}$-NO_2), 154.6 ($\underline{C}$=N). m/z[41] = 179 ($[M+H]^+$, 1-benzyl-3-(*N*,*N*-dimethyl)-urea (**335**)), 149 ($[M+H]^+$, *m*-nitrobenzonitrile (**383**)).

Method 3

Repeating the reaction at the same scale, but employing a ten minute stir time rather than 1 h yielded the crude *oxadiazoline* (0.217 g, 10%) as a pale yellow solid. δ_H: 2.42 [6H, s, N($C\underline{H}_3)_2$], 4.41 (2H, q, J = 16.1, PhC$\underline{H}_2$), 6.14 (1H, s, NC$\underline{H}$ON), 7.15 (2H, m, Ar$\underline{H}$), 7.31 (3H, m, Ar$\underline{H}$), 7.63 (1H, t, J = 8.0, *m*-Ar$\underline{H}$ of *m*-NO_2-Ar), 7.89 (1H, m, *o*-Ar$\underline{H}$ of *m*-NO_2-Ar), 8.31 (1H, m, *p*-Ar$\underline{H}$ of *m*-NO_2-Ar), 8.42 (1H, m, *o*-Ar$\underline{H}$ of *m*-NO_2-Ar).

8.1.1.4 Attempted preparation of 3-(2,4,6-trimethylphenyl)-4-benzyl-5-(*N´,N´*-dimethyl)-Δ²,1,2,4-oxadiazoline 369

Method 1



2,4,6-Trimethylbenzohydroximoyl chloride (0.198 g, 1.00 mmol) in ether (10 mL) was added dropwise to a cooled (<10 ^oC, water/icebath), stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (0.163 g, 1.01 mmol) and triethylamine (0.107 g, 1.05 mmol) in ether (10 mL) over 5 min. The resulting cream coloured solution was warmed to room temperature and stirred overnight. Water (15 mL) was added to the stirring mixture to dissolve the precipitate. The solution was transferred to a separating funnel and the phases were separated. The aqueous layer was washed with ether (1 x 10 mL) and separated. The organic extracts were combined, dried, filtered and concentrated. The resulting yellow oil was placed under high vacuum overnight to remove any residual solvents. ^{1}H NMR spectroscopic analysis gave a mixture of unidentifiable products.

[41]Other solvents were used to try to obtain a parent molecular ion peak without success, [Acetonitrile:methanol & acetonitrile:dimethylsulfoxide].

Method 2

2,4,6-Trimethlybenzohydroximoyl chloride (1.287 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.055 g, 6.5 mmol) and triethylamine (0.66 g, 6.5 mmol) in ether (35 mL). The resulting pale cream solution was warmed to room temperature and stirred for 10 min. The mixture was filtered to remove the precipitate. The solvent was evaporated *in vacuo* to yield a pale yellow solid (1.08 g, 51%). ν_{max}(film): 3028, 2291, 1648, 1434, 1376, 1335 cm^{-1}. ^{1}H NMR spectroscopic analysis showed that dehydrohalogenation did occur as is evident by the formation of mesitonitrile-*N*-oxide (**7**) which has the characteristic signals at 2.30 and 2.42 ppm in the ^{1}H NMR spectrum. However, the cycloaddition did not take place within 10 min as the *N*,*N*-dimethyl-*N´*-benzylformamidine (**339**) (7.38 ppm) and mesitonitrile-*N*-oxide (**7**) were observed.

Method 3 NMR spectroscopy tube reaction

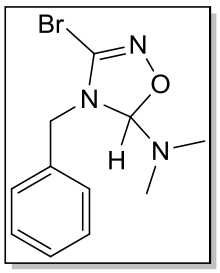
N,*N*-Dimethyl-*N´*-benzylformamidine (33.00 mg, 0.2 mmol) in $CDCl_3$ (0.5 mL) was added to mesitonitrile-*N*-oxide (34.00 mg, 0.2 mmol) in $CDCl_3$-d_1 (0.5 mL). Half of the sample volume was transferred to an NMR spectroscopy tube and topped up to 0.6 mL with $CDCl_3$. The sample in the NMR spectroscopy tube was immediately submitted for ^{1}H NMR spectroscopic analysis. The sample was also monitored over intervals for 17 h by NMR spectroscopy. It showed that the cycloaddition reaction did not take place within 17 h of combining the reactants as indicated by the presence of mesitonitrile-*N*-oxide (**7**) (2.30 & 2.42 ppm) and *N*,*N*-dimethyl-*N´*-benzylformamidine (**339**) (7.38 ppm)

Method 4 NMR spectroscopy tube reaction

Mesitonitrile-*N*-oxide (11.00 mg, 0.07 mmol) was dissolved in $CDCl_3$ (1 mL). ^{1}H NMR of the entire solution was carried out. The $CDCl_3$ solution was then transferred to a sample of *N*,*N*-dimethyl-*N´*-benzylformamidine (12.00 mg, 0.07 mmol). The solution was then mixed and transferred to the NMR spectroscopy tube and submitted for ^{1}H NMR spectroscopic analysis. ^{1}H NMR spectroscopic analysis suggests that the mesitonitrile-*N*-oxide and *N*,*N*-dimethyl-*N´*-benzylformamidine (**339**) did not undergo cycloaddition reaction as only the 3,4-dimesitylfuroxan (**313**) was observed after 65 h of analysis. *N*,*N*-dimethyl-*N´*-benzylformamidine (**339**) appears to have degraded over this time.

8.1.1.5 Attempted preparation of 3-bromo-4-benzyl-5-(*N´,N´*-dimethyl)-Δ^2,1,2,4-oxadiazoline 370

Method 1



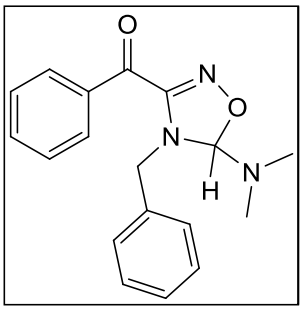
Dibromoformaldoxime (1.32 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring suspension of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.06g, 6.51 mmol) and potassium *t*-butoxide (0.73 g, 6.51 mmol) in ether (35 mL). The yellow cloudy mixture which resulted was warmed to room temperature and stirred for 1 h. The mixture was filtered to remove the solid triethylamine hydrobromide precipitate. The solvent was removed *in vacuo* (without heat) to yield a yellow/orange oil (0.608 g, 33%). The crude sample was placed under high vacuum to remove any residual solvent, however, dimethylformamide (**371**) was the product observed.. ν_{max} (film): 3187, 3066, 3032, 2218, 1666, 1454, 1388, 1098 cm^{-1}; δ_H: 1.25 (2H, s), 2.83 (3H, s, NC<u>H</u>$_3$ **371**), 2.92 (3H, s, NC<u>H</u>$_3$ **371**), 4.15 (1.3H, d, J = 5.6), 5.64 (0.6H, bs), 7.33 (5H, m), 7.53 (0.55H, m), 7.91 (1H, s, C<u>H</u>O **371**), 9.00 (0.11H, s), 9.99 (0.09H, s). m/z = 74 ([M+H]$^+$ **371**).

Method 2

Dibromoformaldoxime (1.32 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.06 g, 6.50 mmol) and triethylamine (0.66 g, 6.54 mmol) in ether (35 mL). A yellow cloudy mixture resulted which was warmed to room temperature and stirred for ten minutes. The solution was then filtered to remove the precipitate and the solvent was evaporated *in vacuo* to yield a pale yellow oil (0.351 g, 19%). ν_{max} (film): 3207, 2217, 1660, 1496, 1454, 1412, 1358, 1254, 1099 cm^{-1}; δ_H: 1.16 (1.72H, m), 1.37 (1H, m), 2.88 (3H, s, NC<u>H</u>$_3$ **371**), 2.96 (3H, s, NC<u>H</u>$_3$ **371**), 3.02 (1H, m), 4.15 (1.20H, bs), 4.42 (0.93H, d, J = 5.5), 7.30 (5.8H, m), 7.92 (0.9H, bs), 8.02 (1H, s, C<u>H</u>O **371**).

8.1.1.6 3-Benzoyl-4-benzyl-5-(*N´,N´*-dimethyl)-Δ²,1,2,4-oxadiazoline 373

Method 1



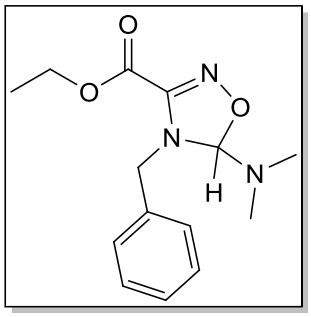
1-Benzoyl-1-chloroformaldoxime (1.19 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 °C, water/icebath), stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.06 g, 6.51 mmol) and triethylamine (0.66 g, 6.50 mmol) in ether (35 mL). The pale orange cloudy mixture which resulted was warmed to room temperature and stirred for 1 h. The precipitate was removed by gravity filtration. The solvent was evaporated *in vacuo* (without heat) to yield the crude *oxadiazoline* (0.89 g, 44%) as pale yellow oil. The sample was placed under high vacuum for 20 min to remove any excess solvent. ν_{max} (film): 3062, 3031, 1657, 1545, 1453, 1292, 1045 cm^{-1}; δ_H: 2.38 [6H, s, N(C<u>H</u>$_3$)$_2$], 4.29 (1H, d, J = 15.6Hz, PhC<u>H</u>$_2$), 5.08 (1H, d, J = 15.6Hz, PhC<u>H</u>$_2$), 6.12 (1H, s, NC<u>H</u>ON), 7.29 (5H, m, Ar<u>H</u>), 7.46 (2H, t, J = 8.1Hz, *m*-Ar<u>H</u>), 7.60 (1H, m, *p*-Ar<u>H</u>), 8.12 (2H, m, *o*-Ar<u>H</u>); δ_C: 36.4 [N(<u>C</u>H$_3$)$_2$], 46.5 (Ph<u>C</u>H$_2$), 107.7 (N<u>C</u>HON), 127.7, 127.8, 128.4, 128.7, 130.5 and 134.1 (6 x Ar<u>C</u>H), 136.0 (*ipso* <u>C</u> of Ar), 136.7 (*ipso* <u>C</u> of Ar), 151.4 (<u>C</u>=N), 183.6 (<u>C</u>=O). m/z = 342 [(M+H+MeOH)$^+$ oxadiazoline (**373**)].

Method 2

1-Benzoyl-1-chloroformaldoxime (1.19 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 °C, water/icebath), stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.06 g, 6.54 mmol) and triethylamine (0.66 g, 6.53 mmol) in ether (35 mL). The yellow cloudy mixture which resulted was stirred at room temperature for ten min, then filtered and the solvent was evaporated *in vacuo* to yield the crude *oxadiazoline* (1.034 g, 51%) as a yellow/orange oil. ν_{max} (film): 3063, 3031, 1663, 1614, 1549, 1453, 1236 cm^{-1}; δ_H: 2.38 [6H, s, N(C<u>H</u>$_3$)$_2$], 4.29 (1H, d, J = 15.8, PhC<u>H</u>$_2$), 5.07 (1H, d, J = 15.8, PhC<u>H</u>$_2$), 6.12 (1H, s, NC<u>H</u>ON), 7.28 (5H, m, Ar<u>H</u>), 7.46 (2H, m, *m*-Ar<u>H</u>), 7.60 (1H, m, *p*-Ar<u>H</u>), 8.12 (2H, m, *o*-Ar<u>H</u>).

8.1.1.7 Attempted preparation of 3-ethoxy-4-benzyl-5-(*N´,N´*-dimethyl)-Δ^2,1,2,4-oxadiazoline 374

Method 1



A solution of ethylchloroglyoxalate oxime (0.99 g, 6.55 mmol) in dry ether (24 mL) was added dropwise to a cooled solution (<10 ^{o}C, water/icebath), stirring solution of *N´*-benzyl-*N*,*N*-dimethylformamidine (1.07 g, 6.6 mmol) and triethylamine (0.68 g, 6.69 mmol) in dry ether (26 mL) over 45 min. A white precipitate formed on addition and the resulting solution was stirred overnight. Water (30 mL) was added to dissolve the precipitate and the phases were separated. The aqueous phase was extracted with ether (30 mL). The combined organic extracts were dried, filtered and the solvent was removed *in vacuo* (without heat). Attempted recrystallization of the residue from cold ethyl acetate and hexane was unsuccessful and evaporation of the solvent gave the *oxadiazoline* as an enriched sample together with furoxan **315** as a yellow oil. ν_{max} (film): 3062, 3029, 1749, 1697, 1635, 1535, 1232 cm^{-1}; δ_H: 1.36 (3H, t, J = 7.3, $CH_2C\underline{H}_3$), 2.34 [6H, s, $N(C\underline{H}_3)_2$], 4.26 (1H, d, J = 15.7, $PhC\underline{H}_2$), 4.35 (2H, qd, J = 7.2, 7.3, $C\underline{H}_2CH_3$), 5.14 (1H, d, J = 15.8, $PhC\underline{H}_2$), 6.08 (1H, s, $NC\underline{H}ON$), 7.29 (5H, m, $Ar\underline{H}$); δ_C: 13.9 ($\underline{C}H_3CH_2O$), 36.4 [$N(\underline{C}H_3)_2$], 46.5 ($Ph\underline{C}H_2$), 62.5 ($CH_3\underline{C}H_2O$), 108.2 ($N\underline{C}HON$), 127.6, 127.7 and 128.7 (3 x $Ar\underline{C}H$), 136.5 (*ipso* $\underline{C}$ of Ar), 146.8 ($\underline{C}_3$ of oxadiazoline), 157.9 ($\underline{C}$=O). ^{1}H NMR spectroscopy shows the presence (15%) of 3,4-diethoxycarbonylfuroxan (**315**) as illustrated by the characteristic signals at 1.42 & 4.48 ppm.

Method 2

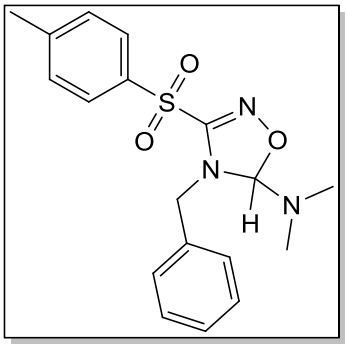
Ethylchloroglyoxalate oxime (0.99 g, 6.5 mmol) in ether (20 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.06 g, 6.51 mmol) and triethylamine (0.66 g, 6.51 mmol) in ether (35 mL). The yellow cloudy mixture which resulted was warmed to room temperature and stirred for 1 h. The mixture was filtered to remove the triethylamine hydrochloride precipitate. The solvent was removed *in vacuo* (without heat) and the crude *oxadiazoline* (0.6 g. 35%) was isolated as yellow oil together with the furoxan **315**. The sample was placed under high vacuum to ensure the removal of any residual solvent. ν_{max} (film): 3088, 3063, 3031, 1730, 1567, 1454, 1304, 1216, 1034 cm^{-1}; δ_H: 1.36 (3H, t, J =

7.1, $CH_2C\underline{H}_3$), 2.33 [6H, s, $N(C\underline{H}_3)_2$], 4.27 (1H, d, J = 15.7, $PhC\underline{H}_2$), 4.35 (2H, qd, J = 7.2, 7.1, $C\underline{H}_2CH_3$), 5.12 (1H, d, J = 15.7, Ph-$C\underline{H}_2$), 6.08 (1H, s, NC<u>H</u>ON), 7.28 (5H, m, Ar<u>H</u>); δ_C: 13.9 ($\underline{C}H_3CH_2O$), 36.4 [$N(\underline{C}H_3)_2$], 46.6 ($Ph\underline{C}H_2$), 62.5 ($CH_3\underline{C}H_2O$), 108.3 (N<u>C</u>HON), 127.6, 127.6 and 128.7 (3 x Ar<u>C</u>H), 136.5 (*ipso* <u>C</u> of Ar), 146.9 ($\underline{C}_3$ of oxadiazoline), 158.0 (<u>C</u>=O). m/z = 278 $[M+H]^+$. ^{1}H NMR spectroscopy shows the presence (22%) of 3,4-diethoxycarbonylfuroxan (**315**) as illustrated by the characteristic signals at 1.42 & 4.48 ppm

Method 3

Ethylchloroglyoxalate oxime (0.99 g, 6.5 mmol) in ether (20 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.07 g, 6.54 mmol) and triethylamine (0.66 g, 6.51 mmol) in ether (35 mL). The white cloudy mixture which resulted was warmed to room temperature and stirred for 10 min. The mixture was filtered to remove the precipitate and the solvent was evaporated *in vacuo* to yield the crude *oxadiazoline* (0.866 g, 48%) as a pale yellow oil. ν_{max} (film): 3088, 3064, 3031, 1731, 1681, 1626, 1567, 1454, 1301, 1233, 1032 cm^{-1}; δ_H: 1.36 (3H, t, J = 7.5, $CH_2C\underline{H}_3$), 2.34 [6H, s, $N(C\underline{H}_3)_2$], 4.26 (1H, d, J = 15.7, $PhC\underline{H}_2$), 4.35 (2H, qd, J = 7.2, 7.3, $C\underline{H}_2CH_3$), 5.13 (1H, d, J = 15.7, $PhC\underline{H}_2$), 6.08 (1H, s, NC<u>H</u>ON), 7.28 (5H, m, Ar<u>H</u>). ^{1}H NMR spectroscopy shows the presence (68%) of 3,4-diethoxycarbonylfuroxan (**315**) as illustrated by the characteristic signals at 1.42 & 4.48 ppm

8.1.1.8 3-(*p*-Toluenesulfonyl)-4-benzyl-5-(*N´,N´*-dimethyl)-Δ²,1,2,4-oxadiazoline 375

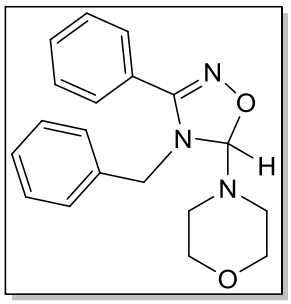


1-*p*-Toluenesulfonyl-1-bromoformaldoxime (1.808 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* a Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*,*N*-dimethyl-*N´*-benzylformamidine (1.06 g, 6.52 mmol) and triethylamine (0.66 g, 6.52 mmol) in ether (35 mL). The pale yellow cloudy mixture which resulted was warmed to room temperature and stirred for 10 min. The mixture was filtered to remove the precipitate and the solvent was removed *in vacuo* to yield the crude *oxadiazoline* (1.1 g, 47%) as an orange oil. Comparison of the ^{1}H NMR spectrum of an authentic sample of the urea and literature data of the nitrile indicates that the oxadiazoline

has been isolated along with tosylcyanide (**377**) and 1-benzyl-3-(*N*,*N*-dimethyl)-urea (**335**) in a ratio of 4:1:1.[199] ν_{max} (film): 3294, 3031, 2949, 2876, 2796, 2691, 2192 (C≡N), 1675, 1622, 1556, 1456, 1339, 1231, 1160, 1120, 1086, 1051, 1031, 962 cm^{-1}; δ_H: 2.23 [6H, s, N(C<u>H</u>$_3$)$_2$], 2.46 (3H, s, ArC<u>H</u>$_3$), 4.27 (1H, d, J = 15.5, PhC<u>H</u>$_2$), 5.13 (1H, d, J = 15.5, PhC<u>H</u>$_2$), 5.94 (1H, s, NC<u>H</u>ON), 7.30 (7H, m, Ar<u>H</u>), 7.88 (2H, d, J = 8.4, *o*-Ar<u>H</u>). Other peaks: 2.35 (1.3H, s), 2.45 (0.7H, s), 2.50 (0.6H, s), 2.87 (0.5H, s), 2.89 (0.6H, s), 4.46 (0.7H, d, J = 6.0), 6.32 (0.3H, bs), 7.18 (0.8H, m), 7.44 (1.1H, t, J = 8.8), 7.57 (0.3H, d, J = 8.0), 7.76 (0.5H, d, J = 8.2), 8.03 (1H, m), 8.25 (0.3H, s). m/z: 181 (M^+, tosylcyanide (**377**)).

8.1.2 Reactions with *N*-benzylformimidoylmorpholine

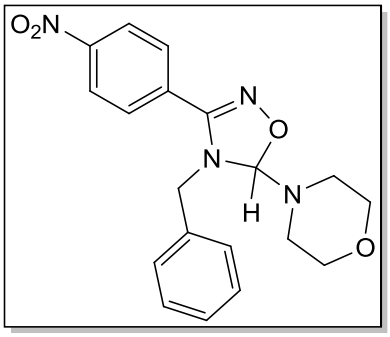
8.1.2.1 Attempted preparation of 3-phenyl-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 380



Benzohydroximoyl chloride (0.156 g, 1.0 mmol) in ether (5 mL) was added dropwise to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (0.206 g, 1.01 mmol) and triethylamine (0.115 g, 1.14 mmol) in ether (5 mL) over 5 min. The white cloudy mixture was warmed to room temperature and stirred overnight. Water (10 mL) was added to the stirring mixture to dissolve the precipitate. The precipitate dissolved immediately on addition to yield a cloudy biphasic solution. The phases were separated and the aqueous layer was extracted with ether (2 x 20 mL). The organic extracts were combined, dried, filtered and the solvent was removed *in vacuo*. The sample was then placed under high vacuum overnight to remove any residual solvent. (0.1381g, 42.7%) Benzonitrile (**175**) and *N*-benzylmorpholine-4-carboxamide (**336**) in a 1:1 ratio were observed. δ_H: 3.36 [4H, t, J = 4.9, N(C<u>H</u>$_2$)$_2$ **336**], 3.68 [4H, t, J = 4.9, O(C<u>H</u>$_2$)$_2$ **336**], 4.43 (2H, d, J = 5.5, PhC<u>H</u>$_2$ **336**), 4.83 (1H, bs, N<u>H</u> **336**), 7.48 (10H, m, Ar<u>H</u> **336** & **175**).

8.1.2.2 3-(*p*-Nitrophenyl)-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 381

Method 1



p-Nitrobenzohydroximoyl chloride (0.204 g, 1.02 mmol) in ether (5 mL) was added dropwise to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (0.208 g, 1.02 mmol) and triethylamine (0.101 g, 1.00 mmol) in ether (10 mL) over 5 min. The solution was warmed to room temperature and stirred overnight. Water (15 mL) was added to the stirring mixture to dissolve the precipitate. The phases were separated and the aqueous layer was washed with ether (2 x 20 mL). The organic extracts were combined, dried, the solvent evaporated and the resulting residue was placed under high vacuum overnight. The crude weight isolated was 0.1873g and the ^{1}H NMR spectroscopic analysis of this shows a small quantity of oxadiazoline, but the sample isolated was predominantly *N*-benzylmorpholine-4-carboxamide (**336**) and *p*-nitrobenzonitrile (**378**). The residue was recrystallised from ethyl acetate/hexane to yield dark yellow solid (177.00 mg, 5%), (Found: C, 61.73; H, 5.87; N, 13.37 $C_{19}H_{20}N_4O_4$ requires C, 61.95; H, 5.47; N, 15.21%). ^{1}H NMR spectroscopic analysis of the recrystallized product showed that *N*-benzylmorpholine-4-carboxamide (**336**) had been isolated.δ_H: 3.37 [4H, m, N(C<u>H</u>$_2$)$_2$ **336**], 3.69 [4H, m, O(C<u>H</u>$_2$)$_2$ **336**], 4.44 (2H, d, J = 5.5, PhC<u>H</u>$_2$ **336**), 4.71 (1H, bs, N<u>H</u> **336**), 7.31 (5H, m, Ar<u>H</u> **336**).

Method 2

p-Nitrobenzohydroximoyl chloride (0.202 g, 1.01 mmol) in ether (10 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (0.204 g, 1.00 mmol) and triethylamine (0.102 g, 1.01 mmol) in ether (10 mL). Following addition, the icebath was removed and the solution was stirred at room temperature for ten minutes. Water (15 mL) was added to the stirring mixture to dissolve the precipitate. The phases were separated and the organic layer was washed with water (2 x 10 mL). A slight emulsion appeared on the first addition of water to the organic phase, so ether (15 mL) was added in an attempt to break it up (fairly successful). The organic extracts were combined dried and the solvent

was evaporated to yield a pale yellow solid (0.2 g, 6%). δ_H: *p*-Nitrobenzonitrile-*N*-oxide (**265**) isolated.

Method 3

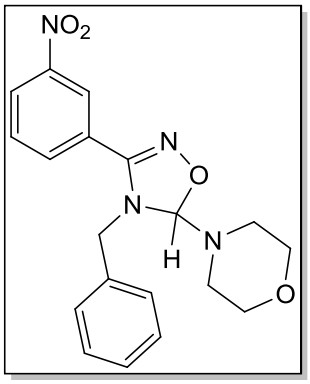
p-Nitrobenzohydroximoyl chloride (1.307 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* a Pasteur pipette, to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (1.33 g, 6.53 mmol) and triethylamine (0.66 g, 6.53 mmol) in ether (35 mL). The cloudy yellow mixture which resulted was warmed to room temperature and stirred for ten min. The mixture was filtered to remove the precipitate and a yellow solution resulted. The solvent was evaporated *in vacuo* without heat to yield a yellow solid (1.1 g, 45%). Comparison of ^1H NMR spectroscopic data with authentic samples of *N*-benzylmorpholine-4-carboxamide (**336**), *p*-nitrobenzonitrile-*N*-oxide (**265**), *p*-Nitrobenzohydroximoyl chloride (**275**), *N*-benzylformimidoylmorpholine (**318**) and oxadiazoline (**381**) show that *N*-benzylmorpholine-4-carboxamide (**336**) was isolated.ν_{max} (film): 3296, 3062, 3032, 1667, 1523, 1453, 1386, 1348, 1113 cm^{-1}; δ_H: 3.39 [1.88H, m, N(C$\underline{H}_2$)$_2$ **336**], 3.56 (1.54H, m), 3.65 (1.57H, m), 3.69 [1.85H, m, O(C$\underline{H}_2$)$_2$ **336**], 4.22 (0.23H, d, J = 6.8), 4.39 (0.51H, d, J = 6.5), 4.48 (2H, d, J = 5.9, PhC$\underline{H}_2$ **336**), 6.08 (1H, bs, N$\underline{H}$ **336**), 7.30 (7.79H, m, Ar$\underline{H}$), 7.62 (0.59H, m), 8.04 (0.92H, bs, Ar$\underline{H}$), 8.17 (0.72H, m), 8.26 (1.1H, bs, Ar$\underline{H}$) m/z = no diagnostic ions.

Method 4 NMR spectroscopy tube reaction

0.07 M Triethylamine solution in $CDCl_3$ (1 mL) was added to a sample vial containing *p*-nitrobenzohydroximoyl chloride (14.00 mg, 0.07 mmol) and that solution was mixed briskly. 0.7 mL of the solution was transferred to an NMR spectroscopy tube and ^1H NMR spectroscopic analysis carried out. Once completed, the NMR spectroscopy tube contents were poured into a sample vial and solution (1 mL) was transferred to a sample vial containing *N*-benzylformimidoylmorpholine (14.30 mg, 0.07 mmol) and that solution was mixed briskly. A 0.7 mL portion of the solution was transferred to an NMR spectroscopy tube and ^1H NMR spectroscopy run. The sample was analysed by ^1H NMR spectroscopy over time. δ_H: 2.68 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 2.84 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.71 [4H, t, J = 4.8, O(C$\underline{H}_2$)$_2$], 4.43 (2H, d, J = 5.3, PhC$\underline{H}_2$), 6.08 (1H, s, NC$\underline{H}$ON), 7.18 (2H, m, Ar$\underline{H}$), 7.34 (3H, m, Ar$\underline{H}$), 7.77 (2H, m, Ar$\underline{H}$), 8.30 (2H, m, Ar$\underline{H}$). The oxadiazoline formed quantitatively on mixing of reactants. Cycloreversion began to occur within 4.75 h to form the *p*-nitrobenzonitrile (**378**) and *N*-benzylmorpholine-4-carboxamide (**336**) in a 1:1 ratio.

Cycloreversion was complete in 128 h. Comparison with an authentic sample of the urea and with literature data of the nitrileconfirmed their presence.[206b]

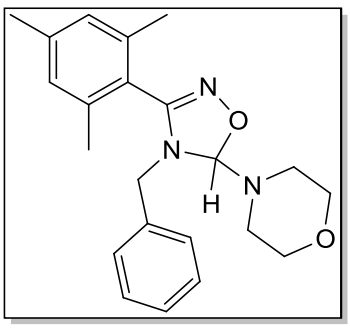
8.1.2.3 3-(*m*-Nitrophenyl)-4-benzyl-5-(4'-morpholino)-Δ²-1,2,4-oxadiazoline 382



m-Nitrobenzohydroximoyl chloride (1.304 g, 6.5 mmol) in ether (30 mL) was added dropwise *via* a Pasteur pipette, to a cooled (<10 °C, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (1.33 g, 6.52 mmol) and triethylamine (0.66 g, 6.53 mmol) in ether (25 mL). The white cloudy mixture which resulted was warmed to room temperature and stirred for ten min. The mixture was then filtered to remove the precipitate and a clear solution resulted. The solvent was evaporated *in vacuo* and a yellow solid (1.68 g, 70%) was isolated. ν_{max} (film): 3278, 3032, 1660, 1531, 1350, 1112 cm^{-1}. The ^1H NMR spectroscopy shows a mixture of *N*-benzylmorpholine-4-carboxamide (**336**) and other unidentifiable peaks.; δ_H: 3.39 (1.90H, m), 3.57 [1.81H, m, N(C<u>H</u>$_2$)$_2$ **336**], 3.64 (1.46H, m), 3.69 (1.65H, m, O(C<u>H</u>$_2$)$_2$ **336**], 3.75 (0.84H, m), 4.40 (0.45H, d, J = 6.5), 4.48 (2H, d, J = 5.9, PhC<u>H</u>$_2$ **336**), 6.02 (1H, bs, N<u>H</u> **336**), 7.30 (8H, m, Ar<u>H</u> **336**), 7.82 (1H, m, Ar<u>H</u>), 8.04 (0.81H, bs), 8.30 (2.44H, m), 8.53 (0.62H, m), 8.90 (0.3H, m), 9.05 (0.3H, m), 9.49 (0.42H, m). m/z = no diagnostic ions observed.

8.1.2.4 Attempted synthesis of 3-(2,4,6-trimethylphenyl)-4-benzyl-5-(4'-morpholino)-Δ²-1,2,4-oxadiazoline 384

Method 1



2,4,6-Trimethylbenzohydroximoyl chloride (0.20 g, 1.01 mmol) in ether (5 mL) was added dropwise to a cooled (<10 °C, water/icebath) stirring solution of *N*-benzylformimidoylmorpholine (0.21 g, 1.02 mmol) and triethylamine (0.10 g, 1.03 mmol) in ether (10 mL). The pale yellow solution which resulted was warmed to room temperature and stirred overnight. Water (25 mL) was added to the stirring mixture to dissolve the precipitate. The phases were separated and the aqueous layer was washed with ether (2 x 20 mL). The organic extracts were combined,

dried, filtered and the solvent was removed *in vacuo*. The sample (0.1847g) was then placed under high vacuum overnight to remove any residual solvent. Recrystallisation from ethyl acetate/hexane yielded a white solid (0.05 mg, 0.01%) which was identified as *N*-benzylmorpholine-4-carboxamide (**336**). δ_H: 3.37 [4H, t, J = 4.9, N(C$\underline{H}_2$)$_2$ **336**], 3.69 [4H, t, J = 4.9, O(C$\underline{H}_2$)$_2$ **336**], 4.44 (2H, d, J = 5.5, PhC$\underline{H}_2$ **336**), 4.68 (1H, bs, N$\underline{H}$ **336**), 7.33 (5H, m, Ar$\underline{H}$ **336**).

Method 2

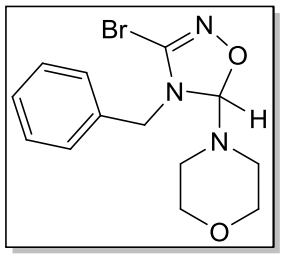
2,4,6-Trimethylbenzohydroximoyl chloride (1.29 g, 6.52 mmol) in ether (20 mL) was added dropwise *via* a Pasteur pipette to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (1.33 g, 6.53 mmol) and triethylamine (0.66 g, 6.52 mmol) in ether (35 mL). The white cloudy mixture which resulted was warmed to room temperature and stirred for ten min. The solution was filtered and the solvent was evaporated *in vacuo* to yield a pale yellow solid (1.8 g, 77%). Comparison of literature data for the nitrile and with an authentic sample of the urea, the ^{1}H NMR spectroscopic data shows that a mixture of *N*-benzylmorpholine-4-carboxamide (**336**) and 2,4,6-trimethylbenzonitrile (**379**) was isolated in a ratio of 33 : 67.[201] ν_{max} (film): 3296 NH of urea?, 3031, 2291, 1671 C=O of urea?, 1436, 1384, 1271, 1113 cm^{-1}; δ_H: 2.30 (3H, bs, ArC$\underline{H}_3$ **379**), 2.40 [6H, s, Ar(C$\underline{H}_3$)$_2$ **379**], 3.32 (0.72H, t, J = 4.7), 3.37 [1.18H, t, J = 3.0, N(C$\underline{H}_2$)$_2$ **336**], 3.56 (*1.19H*, *m*), 3.65 [3.30H, m, O(C$\underline{H}_2$)$_2$ **336** & ?], 4.43 (1H, d, J = 5.9, PhC$\underline{H}_2$ **336**), 6.54 (0.38H, bs, N$\underline{H}$ **336**), 6.90 (2H, bs, Ar$\underline{H}$ **379**), 7.29 (3.24H, m, Ar$\underline{H}$ **336** & ?), 8.02 (0.58H, bs), 8.20 (0.50H, bs).

Method 3 NMR spectroscopy tube reaction

Mesitonitrile-*N*-oxide (10.00 mg, 0.06 mmol) was dissolved in $CDCl_3$ (1 mL) and submitted for ^{1}H NMR spectroscopic analysis. The solution was transferred from the NMR spectroscopy tube to a sample vial containing *N*-benzylformimidoylmorpholine (16.00 mg, 0.08 mmol) and the resulting solution was mixed and transferred to an NMR spectroscopy tube. The sample was submitted for ^{1}H NMR spectroscopic analysis. The sample was analysed by ^{1}H NMR spectroscopy periodically over 360.8 h. These spectra (expt 10-21) were compared to amidine and mesitonitrile-*N*-oxide. On comparison, it appears that the oxadiazoline does not form and the nitrile oxide dimerised even in the presence of the amidine.

8.1.2.5 3-Bromo-4-benzyl-5-(4'-morpholino)-Δ²-1,2,4-oxadiazoline 385

Method 1



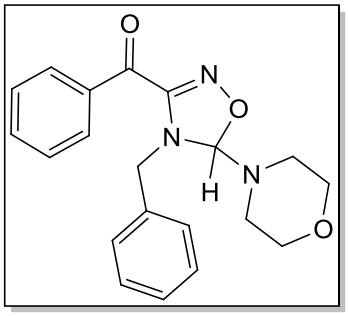
Dibromoformaldoxime (1.32 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (1.34 g, 6.54 mmol) and triethylamine (0.66 g, 6.52 mmol) in ether (35 mL). The cloudy yellow solution which resulted was warmed to room temperature and stirred for ten min. The sample was filtered to remove the precipitate. The solvent was evaporated *in vacuo* and a pale yellow oil (1.17 g, 73%) was isolated. The comparison of ^{1}H NMR spectrum with authentic samples of *N*-formylmorpholine (**340**) & *N*-benzylmorpholine-4-carboxamide (**336**) show that both compounds have been isolated in a 50 : 50 ratio. ν_{max} (film): 2864, 2217, 1661, 1528, 1496, 1452, 1446, 1111 cm^{-1}; δ_H: 3.37 [2H, m, N(C<u>H</u>)$_2$ **336** & **340**], 3.52 [2H, m, N(C<u>H</u>)$_2$ **340**], 3.65 [4.1H, m, O(C<u>H</u>$_2$)$_2$ **336** & **340**], 4.37 (0.5H, d, J = 6.7), 4.43 (2H, d, J = 6.7, PhC<u>H</u>$_2$ **336**), 4.49 (0.15H, s), 6.64 (1H, bs, N<u>H</u> **336**), 7.29 (8H, m, Ar<u>H</u> **336**), 7.98 (0.89H, s, C<u>H</u>O **340**), 8.19 (1.20H, m); m/z = no diagnostic ions.

Method 2

Dibromoformaldoxime (1.32 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring suspension of *N*-benzylformimidoylmorpholine (1.33 g, 6.51 mmol) and potassium *tert*-butoxide (0.73 g, 6.50 mmol) in ether (35 mL). This mixture was warmed to room temperature and stirred for ten min. The mixture was filtered to remove the precipitate. The solvent was removed *in vacuo* to yield a pale orange oil (1.57 g, >100%[42]). The comparison of ^{1}H NMR spectrum with authentic samples of *N*-formylmorpholine (**340**) & *N*-benzylmorpholine-4-carboxamide (**336**) show that both compounds were present in a 50 : 50 ratio. ν_{max} (film): 3231, 2216, 1652, 1453, 1391, 1271, 1113 cm^{-1}; δ_H: 1.28 (8H, s, ^{t}BuOH), 3.38 [3.3H, m, N(C<u>H</u>$_2$) **336** & **340**], 3.53 [3H, m, N(C<u>H</u>$_2$) **340**], 3.66 [7.7H, m, O(C<u>H</u>$_2$)$_2$ **336** & **340**], 4.43 (2H, d, J = 6.0, PhC<u>H</u>$_2$ **336**), 6.78 (1H, bs, N<u>H</u> **336**), 7.29 (8.2H, m, Ar<u>H</u> **336**), 8.00 (1.2H, s, C<u>H</u>O **340**), 8.20 (0.96H, bs), 9.99 (0.66H, s), 11.78 (0.04H, s).

[42] Sample contains *t*-butanol.

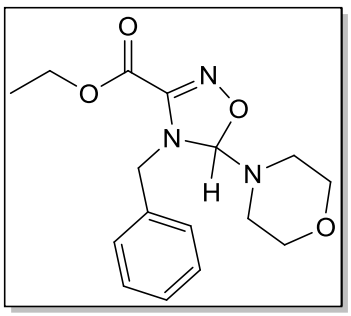
8.1.2.6 Attempted preparation of 3-benzoyl-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 386



1-Benzoyl-1-chloroformaldoxime (1.20 g, 6.55 mmol) in ether (20 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (1.33 g, 6.50 mmol) and triethylamine (0.66 g, 6.52 mmol) in ether (35 mL). The pale yellow cloudy mixture which resulted was warmed to room temperature and stirred for ten min. The mixture was filtered to remove the precipitate which had formed and the solvent was removed from the resulting clear yellow solution *in vacuo* (without heat) to yield a bright yellow/orange oil (1.88 g, 82%). The comparison of ^{1}H NMR spectrum with an authentic sample of *N*-benzylmorpholine-4-carboxamide (**336**) and comparison with literature data of benzoyl cyanide (**387**) show that both compounds have been isolated.[202] The ratio of products is difficult to decipher as the characteristic peaks are overlapping. ν_{max} (film): 3285, 3061, 2285, 1660, 1530, 1450 cm^{-1}; δ_H: 3.37 [1.24H, m, N(C<u>H</u>)$_2$ **336**], 3.55 [1.23H, m], 3.65 [2.29H, m, O(C<u>H</u>$_2$)$_2$ **336** & ?], 3.74 (0.50H, m), 4.32 (0.42H, d, J = 6.5), 4.46 (2H, d, J = 5.9, PhC<u>H</u>$_2$ **336**), 6.12 (1H, bs, N<u>H</u> **336**), 7.31 (7H, m, Ar<u>H</u> **336** & ?), 7.51 (4.16H, m, Ar<u>H</u> **387**), 7.70 (0.89H, m, Ar<u>H</u> **387**), 7.85 (0.98H, m, Ar<u>H</u> **387**), 8.18 (2.37H, m, Ar<u>H</u> **387**); m/z = no diagnostic ions observed.

8.1.2.7 Attempted preparation of 3-ethoxy-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 388

Method 1



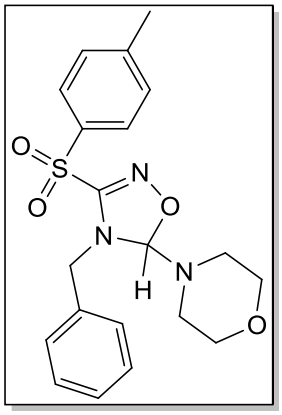
Ethylchloroglyoxalate oxime (0.15 g, 1.01 mmol) in ether (5 mL) was added dropwise to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (0.21 g, 1.01 mmol) and triethylamine (0.11 g, 1.06 mmol) in ether (10 mL) over 5 min. The white solution which resulted was warmed to room temperature and stirred overnight. Water (25 mL) was added to the stirring mixture to dissolve the precipitate. The phases were separated and the aqueous layer was washed with ether (2 x 20 mL) and separated. The organic extracts were combined, dried, filtered and concentrated to yield a yellow oil (0.076 g, 24%). *N*-benzylmorpholine-4-carboxamide (**336**) was observed in the ^{1}H NMR

spectrum. δ_H: 3.37 [4H, m, N(C<u>H</u>$_2$)$_2$ **336**], 3.69 [4H, m, O(C<u>H</u>$_2$)$_2$ **336**], 4.44 (2H, d, J = 5.4, PhC<u>H</u>$_2$ **336**), 4.70 (1H, bs, N<u>H</u> **336**), 7.32 (5H, m, Ar<u>H</u> **336**) and ether.

Method 2

Ethylchloroglyoxalate oxime (0.99 g, 6.5 mmol) in ether (20 mL) was added dropwise *via* Pasteur pipette, to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (1.33 g, 6.5 mmol) and triethylamine (0.66 g, 6.5 mmol) in ether (35 mL). A white cloudy mixture resulted, which was warmed to room temperature and stirred for ten min, then filtered to remove the precipitate. The solvent was removed *in vacuo* to yield a yellow oil (1.5 g, 74%). Comparison of ^{1}H NMR spectrum with authentic samples showed that *N*-benzylformimidoylmorpholine (**318**), 3,4-diethoxycarbonylfuroxan (**315**), ether and triethylammonium chloride were isolated in a ratio of 37.5 : 50 : 8.3 : 4.2. The amidine (**318**) showed characteristic signal at 3.37 ppm and the furoxan (**315**) showed a characteristic signal at 1.42 ppm. ν_{max} (film): 3287, 3062, 3031, 1744, 1662, 1453, 1386, 1112, 1067, 1021 cm^{-1}; δ_H:; m/z = no diagnostic ions.

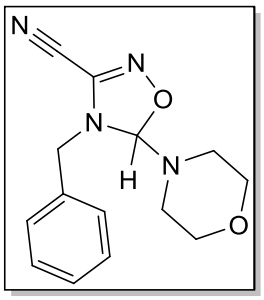
8.1.2.8 3-(*p*-Toluenesulfonyl)-4-benzyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 389



1-*p*-Toluenesulfonyl-1-bromoformaldoxime (1.82 g, 6.53 mmol) in ether (20 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (1.32 g, 6.5 mmol) and triethylamine (0.66 g, 6.5 mmol) in ether (35 mL). The pale cream cloudy mixture which resulted was warmed to room temperature and stirred for ten min. The mixture was filtered to remove the precipitate and the solvent was removed from the resulting clear solution *in vacuo* (without heat) to yield a pale yellow oil (1.8 g, 68%). The comparison of ^{1}H NMR spectrum with authentic samples of *N*-benzylmorpholine-4-carboxamide (**336**), *p*-toluenesulfonylformonitrile-*N*-oxide (**307**), 3,4-*bis*-(*p*-toluenesulfonyl)-furoxan (**309**) and with the literature data of tosylcyanide (**377**) shows that a mixture of these products were isolated.[199] ν_{max} (film): 3285, 2219, 1655, 1496, 1453, 1147 cm^{-1}; δ_H: 2.42 (2.92H, m, **307**/**377**), 2.50 (0.97H, m, **309**/**377**), 3.36 (2.92H, m, N(C<u>H</u>$_2$)$_2$ **336**), 3.53 (1.37H, m), 3.64 (4.3H, m, O(C<u>H</u>$_2$)$_2$ **336**), 4.41 (0.33H, d, J = 7.0), 4.44 (1H, d, J = 5.9, PhC<u>H</u>$_2$ **336**), 4.70 (0.6H, d, J = 6.3), 5.36 (0.28H, t, J = 6.5), 6.46 (0.46H, bs, N<u>H</u> **336**), 7.32 (8H, m, Ar<u>H</u> **336**

& **307**/**377**), 7.79 (2.35H, m, ArH **307**/**377**), 8.02 (0.93H, m), 8.12 (0.18H, m), 8.21 (0.49H, bs); m/z = no diagnostic ions.

8.1.2.9 3-Cyano-4-benzyl-5-(4'-morpholine)-Δ²-1,2,4-oxadiazoline 390

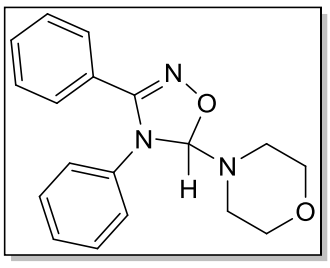


Cyanoformhydroximoyl chloride (0.21 g, 2.00 mmol) in ether (10 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 °C, water/icebath), stirring solution of *N*-benzylformimidoylmorpholine (0.41 g, 2.00 mmol) and triethylamine (0.28 mL, 2.01 mmol) in ether (15 mL). The solution became yellow and cloudy. Following addition, the solution was warmed to room temperature and stirred for 30 min. Water (20 mL) was added and the phases were separated. The organic phase was dried, filtered and solvent evaporated *in vacuo* (without heat) to yield the crude reaction mixture as a yellow oil (0.2686g). NMR spectroscopic analysis shows that *N*-benzylformimidoylmorpholine (**318**), *N*-benzylmorpholine-4-carboxamide (**336**) and oxadiazoline (**390**) were observed. δ_H: 2.60 [2H, m, N(C<u>H</u>$_{ax}$)$_2$ oxadiazoline?), 2.69 (2H, m, N(C<u>H</u>$_{eq}$)$_2$ oxadiazoline?), 3.34 (m, O(C<u>H</u>$_2$) oxadiazoline?), 3.63 (m, O(C<u>H</u>$_2$) oxadiazoline?), 4.36 (1H, d, J = 15.6 Hz, PhC<u>H</u> oxadiazoline), 4.45 (d/m, PhC<u>H</u>$_2$ urea?), 4.51 (1H, d, J = 15.6 Hz, PhC<u>H</u> oxadiazoline), 6.06 (1H, s, NC<u>H</u>ON), 6.37 (0.7H, bs, N<u>H</u> urea?), 7.30 (11H, m, Ar<u>H</u>), 8.21 (0.77H, s, ?); δ_C: 15.26 (Ether), 42.09 (<u>C</u>H$_2$), 45.64 (<u>C</u>H$_2$), 46.16 (<u>C</u>H$_2$), 47.76 (<u>C</u>H$_2$), 59.15 (<u>C</u>H$_2$), 65.83 (<u>C</u>H$_2$ ether), 66.45 (<u>C</u>H$_2$), 66.60 (<u>C</u>H$_2$), 107.40 (<u>C</u>N), 107.50 (N<u>C</u>HON), 126.61 (Ar<u>C</u>H), 127.50 (Ar<u>C</u>H), 127.60 (Ar<u>C</u>H), 127.76 (Ar<u>C</u>H), 128.15 (Ar<u>C</u>H), 128.33 (Ar<u>C</u>H), 128.66 (Ar<u>C</u>H), 128.72 (Ar<u>C</u>H), 129.11 (Ar<u>C</u>H), 134.14 (<u>C</u>H$_2$/4° <u>C</u>), 135.13 (<u>C</u>H$_2$/4° <u>C</u>), 137.71 (<u>C</u>H$_2$/4° <u>C</u>), 141.35 (<u>C</u>H$_2$/4° <u>C</u>), 155.10 (CH), 161.16 (CH), 164.75 (CH).

8.1.3 Reactions with *N*-phenylformimidoylmorpholine

8.1.3.1 3-Phenyl-4-phenyl-5-(4'-morpholino)-Δ²-1,2,4-oxadiazoline 267

Method 1



Benzohydroximoyl chloride (0.99 g, 6.36 mmol) in ether (30 mL) was added dropwise to a cooled (<10 °C, water/icebath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.22 g, 6.44 mmol) and triethylamine (0.67 g, 6.58 mmol) in ether (30 mL) over five min. On addition, a white cloudy mixture resulted, which was warmed to room temperature and stirred for ten minutes.

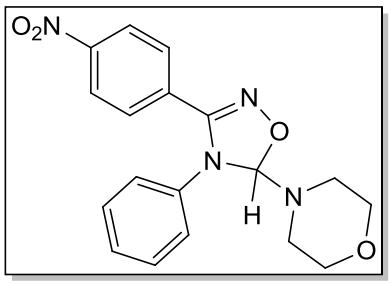
Water (30 mL) was added to the stirring solution to dissolve the triethylamine hydrochloride and a biphasic solution resulted. The organic extract was washed with water (3 x 20 mL). The resulting aqueous phase contained an emulsion/solid, so dichloromethane (50 mL, distilled) was added to try to dissolve it (successfully). The ether extracts and dichloromethane extracts were kept separately and each were dried, filtered and the solvent removed *in vacuo*. The resulting residue was dissolved in ethyl acetate:hexane and placed in a freezer overnight. The recrystallised *oxadiazoline* (0.515 g, 26%) was isolated as a white solid by vacuum filtration. δ_H: 2.79 [2H, m, N(C<u>H</u>$_{ax}$)$_2$], 2.98 [2H, m, N(C<u>H</u>$_{eq}$)$_2$], 3.79 [4H, t, J = 4.77Hz, O(C<u>H</u>$_2$)$_2$], 6.13 (1H, s, NC<u>H</u>ON), 7.10 (3H, m, Ar<u>H</u>), 7.23 (2H, m, Ar<u>H</u>), 7.35 (3H, m, Ar<u>H</u>), 7.51 (2H, m, Ar<u>H</u>); δ_C: 45.0 [N(<u>C</u>H$_2$)$_2$], 67.0 [O(<u>C</u>H$_2$)$_2$], 108.4 (N<u>C</u>HON), 123.0, 125.2, 127.8, 128.7, 129.0 and 130.5 (6 x Ar<u>C</u>H), 132.8 and 139.8 (*ipso* <u>C</u>'s of Ar), 158.2 (N<u>C</u>=N).

Method 2

Benzohydroximoyl chloride (1.01 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^oC, water/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.24 g, 6.50 mmol) and triethylamine (0.66 g, 6.49 mmol) in ether (35 mL). The white cloudy mixture which resulted was warmed to room temperature and stirred for 1 h. The solid precipitate was removed by filtration and the solvent was evaporated *in vacuo* (without heat). A pale cream solid residue was isolated. The sample was placed under high vacuum for 1.5 h. Examination of the proton NMR spectroscopic analysis shows that a morpholine group is present in a 1:1 ratio with the oxadiazoline. The aromatic peaks are also too numerous to correlate to just the oxadiazoline. However, comparison with *N*-phenylmorpholine-4-carboxamide (**395**), *N*-(*N´*-phenylformimidoyl)-morpholine (**341**) and *N*-formylmorpholine (**340**) show that none of these are present. δ_H: 2.78 [2H, m, N(C<u>H</u>$_{ax}$)$_2$], 3.01 [2H, m, N(C<u>H</u>$_{eq}$)$_2$], 3.53 (4H, bs, ?), 3.79 [8H, m, O(C<u>H</u>$_2$)$_2$ 267 & ?], 6.13 (1H, s, NC<u>H</u>ON), 7.27 (19H, m, Ar<u>H</u>).

8.1.3.2 3-(*p*-Nitrophenyl)-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 392

Method 1



p-Nitrobenzohydroximoyl chloride (1.28 g, 6.38 mmol) in ether (30 mL) was added dropwise to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.22 g, 6.39 mmol) and triethylamine (0.66 g, 6.56 mmol) in ether (30 mL) over 15 min. The solution was stirred for 1.25 h. Water (50 mL) was added to the stirring mixture to dissolve the precipitate. A pale yellow emulsion formed so water (50 mL) and ether (50 mL) were added alternatively to see if the emulsion would dissolve/break-up. The solution was transferred to a separating funnel and the phases were separated. The aqueous layer was washed with ether (3 x 50 mL). The organic extracts were combined dried and the solvent was evaporated *in vacuo*. The resulting pale yellow solid was recrystallised from ethyl acetate/hexane and stored in a freezer overnight. The *oxadiazoline* (0.922 g, 41%) was isolated as a pale yellow crystalline solid. δ_H: 2.79 [2H, m, N(C$\underline{H}_{ax}$)$_2$], 2.98 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.81 [4H, t, J = 4.74, O(C$\underline{H}_2$)$_2$], 6.19 (1H, s, NC$\underline{H}$ON), 7.05 (2H, m, Ar$\underline{H}$), 7.19 (1H, m, Ar$\underline{H}$), 7.28 (2H, m, Ar$\underline{H}$), 7.70 (2H, m, *o*-Ar$\underline{H}$), 8.19 (2H, m, *m*-Ar$\underline{H}$); δ_C: 45.0 [N($\underline{C}$H$_2$)$_2$], 66.9 [O($\underline{C}$H$_2$)$_2$], 109.9 (N$\underline{C}$HON), 123.3, 123.9, 126.1, 128.6 and 129.4 (5x Ar$\underline{C}$H), 131.5 and 139.3 (*ipso* $\underline{C}$'s of Ar), 148.7 (Ar$\underline{C}$NO$_2$), 151.7 [N$\underline{C}$(Ar)=N].

Method 2

p-Nitrobenzohydroximoyl chloride (1.29 g, 6.41 mmol) in ether (30 mL) was added dropwise to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.24 g, 6.51 mmol) and triethylamine (0.66 g, 6.5 mmol) in ether (30 mL) over 5 min. The yellow cloudy mixture which resulted was warmed to room temperature and stirred for 10 min. Water (30 mL) was added to dissolve the precipitate. An emulsion formed so organic extract was washed with water (3 x 20 mL). Emulsion/solid present in aqueous layer, therefore dichloromethane (1 x 50 mL) added and the phases separated. The emulsion dispersed and the phases were separated. Each fraction (Ether and dichloromethane) was isolated separately. The organic extracts were combined, dried and the solvent was evaporated *in vacuo*. Both extracts contained the oxadiazoline.

Recrystallisation of the residue from ethyl acetate/hexane afforded the *oxadiazoline* (0.6 g, 29%) as a yellow solid. δ_H: 2.79 [2H, m, N(C$\underline{H}_{ax}$)$_2$], 2.98 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.80 [4H, t, J = 4.75, O(C$\underline{H}_2$)$_2$], 6.19 (1H, s, NC$\underline{H}$ON), 7.05 (2H, m, *o*-Ar$\underline{H}$), 7.24 (3H, m, Ar$\underline{H}$), 7.70 (2H, m, *o*-Ar$\underline{H}$), 8.18 (2H, m, *m*-Ar$\underline{H}$); δ_C: 45.0 [N($\underline{C}$H$_2$)$_2$], 66.9 [O($\underline{C}$H$_2$)$_2$], 109.3 (N$\underline{C}$HON), 123.3, 123.9, 126.1, 128.6 and 129.4 (5 x Ar$\underline{C}$H), 131.5 (*ipso* $\underline{C}$ of Ar), 139.3 (*ipso* $\underline{C}$ of Ar), 148.7 [Ar$\underline{C}$(NO$_2$)], 151.8 (N$\underline{C}$=N).

Method 3

p-Nitrobenzohydroximoyl chloride (1.31 g, 6.52 mmol) in ether (20 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^oC, water/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.24 g, 6.51 mmol) and triethylamine (0.66 g, 6.51 mmol) in ether (35 mL). The yellow cloudy mixture which resulted was warmed to room temperature and stirred for 1 h. The mixture was filtered to remove the precipitate and the solvent was evaporated *in vacuo* (without heat). An orange solid was isolated. The sample was placed under high vacuum for 1.5 h. The crude sample was recrystallised from chloroform:hexane to yield the *oxadiazoline* (0.502 g, 22%) as a yellow solid. δ_H: 2.79 [2H, m, N(C$\underline{H}_{ax}$)$_2$] 2.98 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.80 [4H, t, J = 4.77, O(C$\underline{H}_2$)$_2$], 6.19 (1H, s, NC$\underline{H}$ON), 7.05 (2H, m, *o*-Ar$\underline{H}$), 7.24 (3H, m, Ar$\underline{H}$), 7.70 (2H, m, *o*-Ar$\underline{H}$), 8.18 (2H, m, *m*-Ar$\underline{H}$).

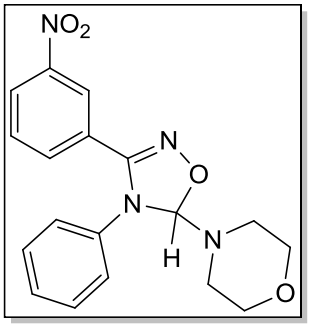
Method 4: NMR spectroscopy tube reaction

Triethylamine (1 mL of 0.07 M solution in $CDCl_3$) was added to *p*-nitrobenzohydroximoyl chloride (14.10 mg, 0.07 mmol) and the resulting solution was briskly stirred. A 0.6 mL portion of the solution was submitted for ^{1}H NMR spectroscopic analysis. Following ^{1}H NMR spectroscopic analysis, the sample in the NMR spectroscopy tube was returned to the sample vial and the entire solution was mixed immediately with *N*-(*N´*-phenylformimidoyl)-morpholine (13.30 mg, 0.07 mmol). Once homogenous, a 0.6 mL portion was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis carried out immediately. δ_H: initial spectrum showed 100% conversion to nitrile oxide, subsequent spectra show some amidine still present, but all of the nitrile oxide has been consumed (within 7 min).

Method 5: NMR spectroscopy tube reaction

p-Nitrobenzonitrile-*N*-oxide (11.60 mg, 0.07 mmol) was dissolved in $CDCl_3$ (1 mL) and a 0.7 mL sample was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis carried out immediately. The entire solution was then combined with *N*-(*N´*-phenylformimidoyl)-morpholine (13.40 mg, 0.07 mmol) and mixed briskly until homogenous. A 0.7 mL sample of this yellow solution was transferred to NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out immediately. The sample was monitored by ^{1}H NMR spectroscopy over time to establish its decomposition rate. δ_H: reaction monitored over 1055 h for decomposition-no decomposition observed.

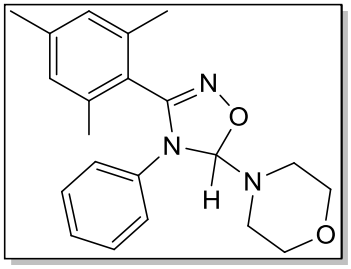
8.1.3.3 3-(*m*-Nitrophenyl)-4-phenyl-5-(4'-morpholino)-Δ²-1,2,4-oxadiazoline 393



m-Nitrobenzohydroximoyl chloride (1.31 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.24 g, 6.51 mmol) and triethylamine (0.66 g, 6.54 mmol) in ether (35 mL). The pale cream cloudy mixture which resulted was warmed to room temperature and stirred for 1 h. The mixture was filtered to remove the precipitate and the solvent was evaporated *in vacuo* without heat. The crude *oxadiazoline* (1.35 g, 59%) was isolated as a pale yellow solid. The sample was placed under high vacuum for 1.5 h. δ_H: 2.79 [2H, m, N(C$\underline{H}_{ax}$)$_2$], 2.97 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.81 [4H, t, J = 4.77, O(C$\underline{H}_2$)$_2$], 6.19 (1H, s, NC$\underline{H}$ON), 7.05 (2H, m, Ar$\underline{H}$), 7.21 (1H, m, Ar$\underline{H}$), 7.27 (2H, m, Ar$\underline{H}$), 7.53 (1H, t, J = 8.02, Ar$\underline{H}$) 7.84 (1H, m, Ar$\underline{H}$), 8.24 (1H, m, Ar$\underline{H}$), 8.35 (1H, m, Ar$\underline{H}$).

8.1.3.4 3-(2,4,6-Trimethylphenyl)-4-phenyl-5-(4'-morpholino)-Δ²-1,2,4-oxadiazoline 394

Method 1



2,4,6-Trimethylbenzohydroximoyl chloride (1.27 g, 6.42 mmol) in dry dichloromethane (30 mL) was added dropwise to a cooled (<10 ^{o}C, water/ice bath), stirring solution of *N*-(*N*-phenylformimidoyl)-morpholine (1.22 g, 6.39 mmol) and

triethylamine (0.66 g, 6.49 mmol) in dry dichloromethane (30 mL) over ten minutes. The resulting solution was stirred for 1 h with the icebath (<10 ^{o}C, water/ice bath) maintained. Water (30 mL) was added to the stirring solution. The phases were separated and the aqueous layer was washed with dichloromethane (3 x 30 mL, dry). The organic extracts were combined, dried, filtered and the solvent was removed *in vacuo*. The sample isolated was pale pink in colour (0.1 g, 5%). ^{1}H NMR spectroscopic analysis indicated that the amidine starting material was still present. This, along with the absence of the oxadiazoline peak implies that the mesitonitrile-*N*-oxide may not react at <10 ^{o}C (water/ ice bath).

Method 2

2,4,6-Trimethylbenzohydroximoyl chloride (1.29 g, 6.41 mmol) in ether (20 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.24 g, 6.51 mmol) and triethylamine (0.66 g, 6.52 mmol) in ether (35 mL). The pale cream cloudy mixture which resulted was warmed to room temperature and stirred for 1 h. The solution was filtered and the solvent was evaporated *in vacuo* (without heat). The crude reaction mixture (2.1 g, 94%) was isolated as a white solid. δ_H: shows *N*-(*N´*-phenylformimidoyl)-morpholine (**341**) (7.51 ppm) and 2,4,6-trimethylbenzonitrile oxide (**7**) (2.30, 2.42 and 6.91 ppm) starting materials. m/z = 191 (100%, **341**).

Method 3

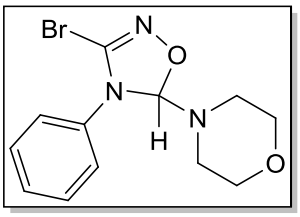
2,4,6-Trimethylbenzohydroximoyl chloride (1.28 g, 6.46 mmol) in dry dichloromethane (30 mL) was added dropwise to a stirring solution of *N*-(*N*-phenylformimidoyl)-morpholine (1.22 g, 6.41 mmol) and triethylamine (0.65 g, 6.46 mmol) in dry dichloromethane (30 mL) at room temperature over ten minutes. The resulting solution was stirred overnight. Water (30 mL) was added to the stirring solution. The phases were separated and the aqueous layer was washed with dichloromethane (30 mL). The organic extracts were combined, dried, filtered and the solvent was removed *in vacuo* to yield a pale orange residue. This residue was recrystallised from dichloromethane:hexane and the resulting solution placed in a freezer. The isolated sample was a pale yellow crystalline solid (0.2 g, 7%). ^{1}H NMR spectroscopy indicated that *N*-(*N´*-phenylformimidoyl)-morpholine (**341**) (7.51 ppm) is still present. This, along with the absence of the oxadiazoline peak implies that the mesitonitrile-*N*-oxide (**7**) may not react at room temperature.

Method 4: NMR spectroscopy tube reaction

Mesitonitrile-*N*-oxide (11.00 mg, 0.068 mmol) was dissolved in $CDCl_3$ (1 mL) and sample submitted for ^1H NMR spectroscopy analysis. The sample was then transferred from the NMR spectroscopy tube to a sample vial containing *N*-(*N´*-phenylformimidoyl)-morpholine (13.00 mg, 0.068 mmol) and solution was transferred back to the NMR spectroscopy tube and shaken. Sample submitted for ^1H NMR spectroscopic analysis and was analysed over 360 h (15 days). The spectra showed that the sample contained the *N*-(*N´*-phenylformimidoyl)-morpholine **(341**) (7.51 ppm) and mesitonitrile-*N*-oxide (**7**) (2.30, 2.42 and 6.91 ppm) starting materials after this time.

8.1.3.5 3-Bromo-4-phenyl-5-(4'-morpholino)-Δ²-1,2,4-oxadiazoline 396

Method 1



Dibromoformaldoxime (1.32 g, 6.53 mmol) in doubly distilled dichloromethane (50 mL) was added dropwise to a cooled (<10 ^oC, water/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.24 g, 6.54 mmol) and triethylamine (0.66 g, 6.51 mmol) in doubly distilled dichloromethane (50 mL) over 15 min. The ice bath was removed and the resulting orange solution was stirred at room temperature for ten min. Water (30 mL) was added to dissolve the precipitate. The biphasic solution was transferred to a separating funnel and the phases were separated. The organic phase was further extracted with water (1 x 50 mL). The organic phase was dried, filtered and the solvent removed *in vacuo* (without heat) to yield a brown oil. The attempted crystallisation of the residue from ethyl acetate-hexane yielded a brown sticky solid (0.242 g, 18%[43]). Examination of the proton NMR spectrum indicated that neither *N*-phenylmorpholine-4-carboxamide (**395**) nor *N*-formylmorpholine (**340**) were present. δ_H: 1.24 (4H, m), 3.39 (2H, m), 3.57 (2.8H, m), 3.68 (7.2H, m), 3.76 (6H, m), 7.11 (1.3H, t, J = 7.28), 7.18 (2.5H, m), 7.30 (3.6H, m), 7.81 (1.9H, s), 8.06 (1.2H, s).

Method 2

Dibromoformaldoxime (1.59 g, 7.82 mmol) in ether (20 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 ^oC, water/ice bath), stirring suspension of *N*-(*N´*-phenylformimidoyl)-morpholine (1.25 g, 6.57 mmol) and potassium *t*-

[43] Contains ethyl acetate and hexane.

butoxide (0.73 g, 6.51 mmol) in ether (35 mL). The resulting pink/brown mixture was warmed to room temperature and stirred overnight. The mixture was filtered to remove the solid residue and solvent evaporated *in vacuo* to yield a brown solid. Spiking the proton NMR spectroscopic sample with *N*-formylmorpholine (**340**) aided the confirmation of its presence. ν_{max} (film): 3099, 2240, 1658, 1600, 1491, 1441, 1272 cm^{-1}; δ_H: 3.41 [1.92H, t, J = 4.86, N(C$\underline{H}_{ax}$)$_2$], 3.58 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.97 [4H, m, O(C$\underline{H}_2$)$_2$], 7.36 (4.24H, m), 8.06 (1H, s, NC$\underline{H}$O).

Method 3

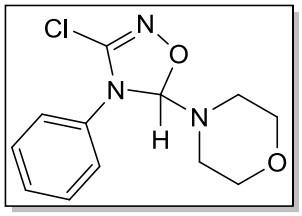
Dibromoformaldoxime (1.32 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 ^oC, water/ice bath), stirring suspension of *N*-(*N´*-phenylformimidoyl)-morpholine (1.24 g, 6.51 mmol) and potassium *t*-butoxide (0.73 g, 6.50 mmol) in ether (35 mL). The pale brown mixture which resulted was warmed to room temperature and stirred for 1 h. The mixture was filtered to remove the solid residue and the solvent was evaporated *in vacuo* (without heat). The sample was dried under high vacuum for 1 h. The residue was recrystallised from chloroform:hexane and isolated as a pale brown solid (0.691 g, 34%). Comparison of the proton NMR data with an authentic sample of *N*-formylmorpholine (**340**) indicated its presence. δ_H: 3.41 [2H, m, N(C$\underline{H}_{ax}$)$_2$], 3.58 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.69 [4H, m, O(C$\underline{H}_2$)$_2$], 7.03 (2H, m, Ar$\underline{H}$), 7.43 (4H, m, Ar$\underline{H}$), 8.06 (1H, s, C$\underline{H}$O).

Method 4

A solution of dibromoformaldoxime (0.66 g, 3.25 mmol) in ether (10 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 ^oC, water/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (0.62 g, 3.25 mmol) and triethylamine (0.46 mL, 3.3 mmol) in ether (15 mL). The resulting green/brown mixture was warmed to room temperature and stirred for 10 min. The reaction mixture was filtered to remove the solid residue and the solvent was evaporated *in vacuo* to yield a brown/green solid, (0.434 g, 43%). The presence of *N*-formylmorpholine (**340**) was confirmed by spiking with a reference sample. δ_H: 3.40 [1.87H, t, J = 4.86, N(C$\underline{H}_{ax}$)$_2$ of **340**], 3.64 [9.67H, m, incl. N(C$\underline{H}_{eq}$)$_2$ of **340**], 3.76 [6.48H, m, incl. O(C$\underline{H}_2$)$_2$ of **340**], 7.07 (5.1H, m), 7.29 (5H, m), 7.64 (1.86H, s), 8.06 (1H, s, NC$\underline{H}$O of **340**)..

8.1.3.6 3-Chloro-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 397

Method 1



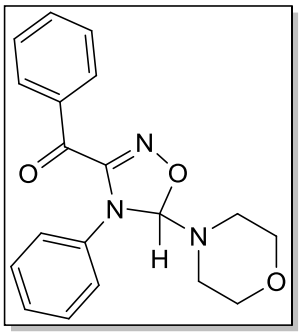
A solution of dichloroformaldoxime (~5.2 mmol [100% yield]) in 1,2-dimethoxyethane (5 mL) and ether (10 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (0.99 g, 5.21 mmol) and triethylamine (0.73 mL, 5.24 mmol) in ether (25 mL). The cloudy brown/red solution was washed through the pressure-equalising addition funnel with ether (~5 mL). The resulting cloudy pale orange/yellow solution was warmed to room temperature and stirred for ten minutes. The mixture was filtered to remove the precipitate and the solvent was removed *in vacuo* to yield a red/brown liquid. ν_{max} (film): 2966, 1710, 1629, 1588, 1492, 1433, 1359, 1171, 1113 cm^{-1}. ^{1}H NMR spectroscopic analysis indicated that *N*-(*N´*-phenylformimidoyl)-morpholine (**341**) and 1,2-dimethoxyethane were the products of this reaction. δ_H: 2.70 (3.3H, s), 3.39 (16.7H, s, 1,2-dimethoxyethane), 3.53 [14H, s and bs overlapping, N(C$\underline{H}_2$)$_2$ **341** and 1,2-dimethoxyethane], 3.74 [4H, t, J = 4.88, O(C$\underline{H}_2$)$_2$ **341**], 6.96 (2H, m, Ar$\underline{H}$ **341**), 7.02 (1H, m, Ar$\underline{H}$ **341**), 7.26 (2H, m, Ar$\underline{H}$ **341**), 7.52 (1H, s, N=C$\underline{H}$ **341**).

Method 2

A solution of dichloroformaldoxime (1.67 g, 14.64 mmol) in ether (16 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (0.99 g, 5.19 mmol) and triethylamine (0.73 mL, 5.24 mmol) in ether (24 mL). The resulting orange solution was stirred at room temperature for 20 min, filtered, solvent removed *in vacuo* to yield a brown oil (1.49 g). ^{1}H NMR spectroscopic analysis indicated that *N*-(*N´*-phenylformimidoyl)-morpholine (**341**) was the product of this reaction. δ_H: 1.21 [4.3H, t, J = 7.11, C$\underline{H}_2$ ether], 2.70 (1.86H, s, ?), 2.84 (1.85H, q, J = 7.27, ?), 3.48 [4.69H, overlapping bs & m, N(C$\underline{H}_2$)$_2$ **341** and ether], 3.74 [4H, m, O(C$\underline{H}_2$)$_2$ **341**], 6.96 (2H, m, Ar$\underline{H}$ **341**), 7.02 (1H, m, Ar$\underline{H}$ **341**), 7.26 (2H, m, Ar$\underline{H}$ **341**), 7.51 (1H, s, N=C$\underline{H}$ **341**). m/z = 191 (M+H)$^{+}$ **341**.

8.1.3.7 3-Benzoyl-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 398

Method 1



1-Benzoyl-1-chloroformaldoxime (1.18 g, 6.43 mmol) in ether (50 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<0 ^{o}C, salt/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.22 g, 6.41 mmol) and triethylamine (0.65 g, 6.39 mmol) in ether (40 mL) over 1.5 h. The resulting mixture was stirred for 10 min. Water (50 mL) was added and the layers were separated. The aqueous layer was further extracted with ether (30 mL) and the combined organic extracts were dried and the solvent removed *in vacuo*. The residue was recrystallised from ethyl acetate/hexane. The pale yellow solid *oxadiazoline* (0.842 g, 39%) was isolated by vacuum filtration, m.p. 94-95.5 ^{o}C. ν_{max} (film): 3321, 3061, 2966, 2919, 1679, 1637, 1598, 1537, 1444, 1248, 1115 cm^{-1}; δ_H: 2.75 [2H, m, N(C$\underline{H}_{ax}$)$_2$], 3.00 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.77 [4H, t, J = 4.76, O(C$\underline{H}_2$)$_2$], 6.26 (1H, s, NC$\underline{H}$NO), 7.09 (2H, m, Ar$\underline{H}$), 7.17 (1H, m, Ar$\underline{H}$), 7.31 (2H, m, Ar$\underline{H}$), 7.53 (2H, m, Ar$\underline{H}$), 7.69 (1H, m, Ar$\underline{H}$), 8.22 (2H, m, Ar$\underline{H}$); δ_C: 44.6 [N($\underline{C}$H$_2$)$_2$], 66.8 [O($\underline{C}$H$_2$)$_2$], 108.4 (N$\underline{C}$HON), 121.4, 125.6, 128.7, 129.2, 130.6 and 134.7 (6 x Ar$\underline{C}$H), 135.2 and 138.3 (2 x *ipso* $\underline{C}$ of Ar), 150.8 ($\underline{C}$=N), 181.6 ($\underline{C}$=O). HRMS (ESI$^+$) exact mass calculated for $C_{11}H_{14}N_2O_2$ [(M+H)$^+$], 207.1134, found 207.1134 for *N*-phenylmorpholine-4-carboxamide (**395**).

Method 2

1-Benzoyl-1-chloroformaldoxime (1.19 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<0 ^{o}C, salt/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.24 g, 6.50 mmol) and triethylamine (0.66 g, 6.50 mmol) in ether (35 mL). The pale yellow/cream mixture which resulted was warmed to room temperature and stirred for 1 h. The reaction mixture was filtered to remove the precipitate and the solvent was removed *in vacuo* (without heat) to yield the crude oxadiazoline as a yellow solid. The sample was dried further under high vacuum for 1 h. The crude residue was recrystallised from chloroform-hexane. The *oxadiazoline* (0.540 g, 25%) was isolated as a yellow solid, m.p. 95-95.5 ^{o}C. ν_{max} (film): 1663, 1549, 1496, 1220, 1115 cm^{-1}; δ_H: 2.75 [2H, m, N(C$\underline{H}_{ax}$)$_2$], 3.00 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.76 [4H, m, O(C$\underline{H}_2$)$_2$], 6.25 (1H, s, NC$\underline{H}$NO), 7.11 (2H, m, Ar$\underline{H}$), 7.26 (3H, m, Ar$\underline{H}$), 7.52

(2H, m, ArH), 7.67 (1H, m, ArH), 8.22 (2H, m, ArH). HRMS (ESI^+) exact mass calculated for $C_{19}H_{19}N_3O_3$ [$(M+H)^+$], 338.1505, found 338.1499.

Method 3

A solution of 1-benzoyl-1-chloroformaldoxime (0.60 g, 3.25 mmol) in ether (10 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^oC, water/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (0.62 g, 3.25 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). The resulting cloudy yellow solution was warmed to room temperature and stirred for 10 min. The mixture was filtered to remove the precipitate and the solvent removed *in vacuo* (without heat) to yield the crude oxadiazoline (0.945g) as a yellow solid. The crude residue was recrystallised from cold chloroform/hexane and placed in the freezer overnight. The *oxadiazoline* (128.00 mg, 12%) isolated as a solid, m.p. 116-122 ^oC. ν_{max} (film): 2964, 2853, 1664, 1599, 1550, 1496, 1220, 1116 cm^{-1}; δ_H: 2.76 [2H, m, N(CH$_{ax}$)$_2$], 3.00 [2H, m, N(CH$_{eq}$)$_2$], 3.77 [4H, t, J = 4.77, O(CH$_2$)$_2$], 6.26 (1H, s, NCHNO), 7.08 (2H, m, N-ArH), 7.17 (1H, m, N-ArH), 7.29 (2H, m, N-ArH), 7.53 (2H, m, ArH), 7.68 (1H, m, ArH), 8.23 (2H, m, ArH); δ_C: 44.7 [N(CH$_2$)$_2$], 66.8 [O(CH$_2$)$_2$], 108.4 (NCHON), 121.4, 125.6 and 129.2 (3 x N-ArCH), 128.7, 130.6 and 134.7 (3 x ArCH), 135.2 and 138.3 (2 x *ipso* C of Ar), 150.8 (C=N), 181.7 (C=O); m/z = 338 $[M+H]^+$.

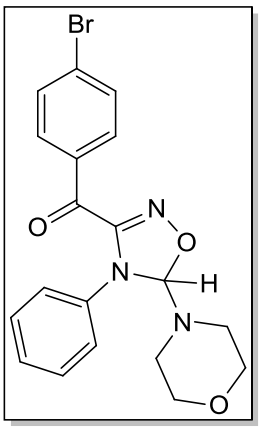
Method 4: NMR spectroscopy tube reaction

1-Benzoyl-1-chloroformaldoxime (12.90 mg, 0.07 mmol) was combined with 0.07 M triethylamine solution in $CDCl_3$ (1 mL) and the solution was mixed briskly. A 0.6 mL sample of this solution was transferred to an NMR spectroscopy tube and a ^1H NMR spectrum run immediately (1:1 ratio of nitrile oxide : furoxan). The contents of NMR spectroscopy tube were returned to the sample vial and the resulting solution (1 mL) was combined with *N*-(*N´*-phenylformimidoyl)-morpholine (13.40 mg, 0.07 mmol) and was mixed briskly. A 0.6 mL sample of this solution was transferred to an NMR spectroscopy tube and ^1H NMR spectroscopy run immediately. The NMR spectroscopy tube was then spiked with a solution of freshly synthesised oxadiazoline in $CDCl_3$. δ_H: 2.68 [2H, m, N(CH$_{ax}$)$_2$ **398**], 2.92 [2H, m, N(CH$_{eq}$)$_2$ **398**], 3.45 [12.18H, bs, N(CH$_2$)$_2$ **341**], 3.68 [17.94H, m, O(CH$_2$)$_2$ **341** and O(CH$_2$)$_2$ **398**], 6.18 (1H, s, NCHON **398**), 6.89 (6.34H, m, ArH **341**), 6.96 (3.27H, m, ArH **341**), 7.03 (2H, m, ArH **398**), 7.10 (1H, m, ArH **398**), 7.19 (9.20H, m, ArH **341** and ArH **398**) 7.47 (10.90H, m, ArH **314**, ArH **398** and CH=N **341**), 7.63

(3.87H, m, ArH **398** and ArH **314**), 7.79 (2.48H, m, ArH **314**), 8.14 (4.89H, m, ArH **314** and ArH **398**). Ratio of 3,4-dibenzoylfuroxan (**314**) : oxadiazoline (**398**) : *N*-(*N´*-phenylformimidoyl)-morpholine (**341**) (23 : 19 : 58).

8.1.3.8 3-(*p*-Bromobenzoyl)-4-phenyl-5-(4'-morpholino)-Δ²-1,2,4-oxadiazoline 399

Method 1



A solution of 1-(*p*-bromobenzoyl)-1-chloroformaldoxime (0.86 g, 3.26 mmol) in ether (10 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (0.62 g, 3.25 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). The resulting mixture was warmed to room temperature and stirred for 10 min. The mixture was filtered to remove the precipitate with the aid of additional ether (10 mL) and the solvent was removed *in vacuo* (without heat) to yield a yellow/pale orange solid, (1.287 g). The *oxadiazoline* (677.00 mg, 50%) was recrystallised from chloroform:hexane and isolated by vacuum filtration as a pale orange/yellow solid, m.p. 90-92 ^{o}C. ν_{max} (film): 3097, 3061, 1673, 1597, 1546, 1499, 1427, 1323, 1259, 1160, 1117, 1099, 1029, 1010 cm^{-1}; $\delta_{H(DMSO\text{-}d6)}$: 2.72 [4H, m, N(C<u>H</u>$_2$)$_2$], 3.62 [4H, bs, O(C<u>H</u>$_2$)$_2$], 6.58 (1H, s, NC<u>H</u>ON), 7.16 (3H, m, N-Ar<u>H</u>), 7.33 (2H, m, N-Ar<u>H</u>), 7.83 (2H, m, *o*-Ar<u>H</u>), 8.05 (2H, m, *m*-Ar<u>H</u>); $\delta_{C(DMSO\text{-}d6)}$: 44.2 [N(<u>C</u>H$_2$)$_2$], 65.9 [O(<u>C</u>H$_2$)$_2$], 107.5 (N<u>C</u>HON), 121.7, 125.3 and 129.0 (3 x Ar<u>C</u>H of N-Ph), 129.3 (Ar<u>C</u>Br), 131.9 and 132.1 (2 x Ar<u>C</u>H), 133.8 and 137.7 (2 x *ipso* <u>C</u> of Ar), 150.3 (<u>C</u>=N), 180.8 (<u>C</u>=O). m/z = 418 (M^{+} ^{81}Br), 416 (M^{+} ^{79}Br). HRMS (ESI^{+}) exact mass calculated for $C_{19}H_{18}N_3O_3Br$ $[M+H]^{+}$ 416.0610, found 207.1125 $[(M+H)^{+}$ *N*-phenylmorpholine-4-carboxamide (**395**)].

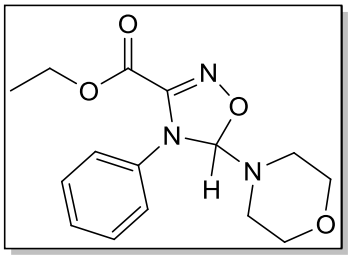
Method 2: NMR spectroscopy tube reaction

0.07 M Triethylamine solution in $CDCl_3$ (1 mL) was added to a sample vial containing 1-(*p*-bromobenzoyl)-1-chloroformaldoxime (18.40 mg, 0.07 mmol) and a 0.7 mL quantity of the solution was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out. The contents of this NMR spectroscopy tube were returned to the original solution and the entire solution was transferred to sample vial containing *N*-(*N´*-phenylformimidoyl)-morpholine (13.30 mg, 0.07 mmol). A 0.7 mL portion of the resulting

solution was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out immediately. δ_H: 1.40 (32H, t, C<u>H</u>$_3$ triethylammonium chloride), 3.10 (21H, q, C<u>H</u>$_2$ triethylammonium chloride), 7.49 (0.76H, m, ?), 7.72 (7H, m, **430**/**431**), 7.91 (2H, m, **431**), 8.09 (2H, m, **430**). The first proton NMR spectrum shows complete conversion to *p*-bromobenzoylnitrile-*N*-oxide (**430**) or 3,4-*bis*-(*p*-bromobenzoyl)-furoxan (**431**) or a mixture of both. The next proton NMR spectrum taken directly after the mixing of the 1,3-dipole and dipolarophile illustrates that a mixture of *N*-(*N´*-phenylformimidoyl)-morpholine (**341**) and 3,4-*bis*-(*p*-bromobenzoyl)-furoxan (**431**) were observed in a 1 : 1 ratio. δ_H: 1.39 (9.4H, t, C<u>H</u>$_3$ triethylammonium chloride), 3.09 (6.3H, q, C<u>H</u>$_2$ triethylammonium chloride), 3.53 [3.3H, m, N(C<u>H</u>$_2$)$_2$ **341**], 3.75 [4.2H, m, O(C<u>H</u>$_2$)$_2$ **341**], 7.01 (3H, m, Ar<u>H</u> **341**), 7.27 (2.4H, m, Ar<u>H</u> **341**), 7.55 (1H, s, N=C<u>H</u> **341**), 7.71 (2H, m, **431**), 7.92 (0.27H, m, **431**), 8.09 (0.87H, m, **431**).

8.1.3.9 3-Ethoxy-4-phenyl-5-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 400

Method 1



Ethylchloroglyoxalate oxime (0.97 g, 6.42 mmol) in ether (30 mL) was added dropwise to a cooled (<10 ^{o}C water/ice bath), stirring solution of *N*-(*N*-phenylformimidoyl)-morpholine (1.24 g, 6.54 mmol) and triethylamine (0.66 g, 6.48 mmol) in ether (30 mL) over 5 min. The cloudy white solution which resulted was warmed to room temperature and stirred for 10 min. Water (30 mL) was added to dissolve the precipitate. The phases were separated and the organic extract was washed with water (3 x 20 mL). The organic extracts were combined, dried and the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate/hexane and the recrystallised *oxadiazoline* (0.192 g, 10%) was isolated as a white crystalline solid, m.p. 105-105.5 ^{o}C. ν_{max} (film): 3454, 2963, 2853, 1739, 1568, 1500, 1431, 1318, 1261, 1207, 1117 cm^{-1}; δ_H: 1.30 (3H, t, J = 7.14, OCH$_2$C<u>H</u>$_3$), 2.74 [2H, m, N(C<u>H</u>$_{ax}$)$_2$], 2.96 [2H, m, N(C<u>H</u>$_{eq}$)$_2$], 3.76 [4H, t, J = 4.78, O(C<u>H</u>$_2$)$_2$], 4.32 (2H, q, J = 7.13, OC<u>H</u>$_2$CH$_3$), 6.17 (1H, s, NC<u>H</u>ON), 7.15 (2H, m, Ar<u>H</u>), 7.24 (1H, m, Ar<u>H</u>), 7.35 (2H, m, Ar<u>H</u>). δ_C: 13.9 (OCH$_2$<u>C</u>H$_3$), 44.8 [N(<u>C</u>H$_2$)$_2$], 62.8 (O<u>C</u>H$_2$CH$_3$), 66.8 [O(<u>C</u>H$_2$)$_2$], 109.6 (N<u>C</u>HON), 122.7 and 129.2 (2 x Ar<u>C</u>H), 126.3 (*p*-Ar<u>C</u>), 138.6 (*ipso* <u>C</u> of Ar), 146.7 (<u>C</u>$_3$ of oxadiazoline), 157.2 (<u>C</u>=O). HRMS (ESI$^+$) exact mass calculated for $C_{15}H_{19}N_3O_4$ [(M+H)$^+$], 306.1454, found 306.1464.

Method 2

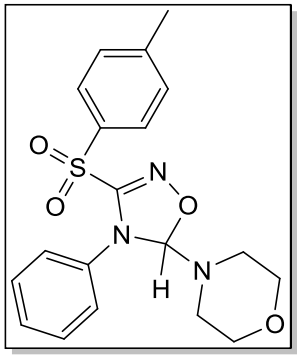
Ethylchloroglyoxalate oxime (0.99 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 ^{o}C water/ice bath), stirring solution of *N*-(*N*-phenylformimidoyl)-morpholine (1.24 g, 6.51 mmol) and triethylamine (0.66 g, 6.52 mmol) in ether (35 mL). The white cloudy mixture which resulted was warmed to room temperature and stirred for 1 h. The mixture was filtered to remove the precipitate and the solvent was removed *in vacuo* (without heat) to yield a white solid. The sample was dried under high vacuum for 1 h. Recrystallisation from chloroform and hexane yielded the *oxadiazoline* (0.1 g, 56%) as a white crystalline solid, m.p. 105-106 ^{o}C. δ_H: 1.30 (3H, t, J = 7.14, $OCH_2C\underline{H}_3$), 2.73 [2H, m, $N(C\underline{H}_{ax})_2$], 2.96 [2H, m, $N(C\underline{H}_{eq})_2$], 3.76 [4H, t, J = 4.77, $O(C\underline{H}_2)_2$], 4.32 [2H, q, J = 7.13, $OC\underline{H}_2CH_3$], 6.17 (NC<u>H</u>ON), 7.14 (2H, m, Ar<u>H</u>), 7.25 (1H, m, Ar<u>H</u>), 7.36 (2H, m, Ar<u>H</u>); δ_C: 13.9 ($OCH_2\underline{C}H_3$), 44.7 [$N(\underline{C}H_2)_2$], 62.8 ($O\underline{C}H_2CH_3$), 66.8 [$O(\underline{C}H_2)_2$], 109.6 (N<u>C</u>HON), 122.7, 126.3 and 129.2 (3 x Ar<u>C</u>H), 138.5 (*ipso* <u>C</u> of Ar), 146.7 ($\underline{C}_3$ of oxadiazoline), 157.2 (<u>C</u>=O). m/z = 306 $[M+H]^+$. HRMS (ESI^+) exact mass calculated for $C_{15}H_{19}N_3O_4$ $[(M+H)^+]$, 306.1454, found 306.1449.

Method 3: NMR spectroscopy tube reaction

Ethylchloroglyoxalate oxime (10.70 mg, 0.07 mmol) was combined with 0.07 M triethylamine solution (1 mL, $CDCl_3$) and the solution was mixed briskly. A 0.6 mL portion of this solution was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out. The contents of the NMR spectroscopy tube poured into the sample vial and its entire contents were combined with *N*-(*N*-phenylformimidoyl)-morpholine (13.40 mg, 0.07 mmol). The resulting solution was mixed briskly, a 0.6 mL portion of this solution was transferred to an NMR spectroscopy tube and the ^{1}H NMR analysed immediately. Subsequent NMR spectroscopic analysis was carried out to monitor the reaction over time. The ^{1}H NMR spectroscopic data showed that the nitrile oxide dimerised prior to the addition of the amidine. The subsequent NMR spectra showed that 3,4-diethoxycarbonylfuroxan (**315**) and *N*-(*N*-phenylformimidoyl)-morpholine (**341**) were present in equal quantities over time.

8.1.3.10 3-(*p*-Toluenesulfonyl)-4-phenyl-5-(4'-morpholino)-Δ²-1,2,4-oxadiazoline 401

Method 1



1-*p*-Toluenesulfonyl-1-bromoformaldoxime (1.81 g, 6.50 mmol) in ether (50 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (1.24 g, 6.52 mmol) and triethylamine (0.66 g, 6.49 mmol) in ether (50 mL). On addition, a pale yellow precipitate formed and the mixture was stirred for 5 min. Water (50 mL) was added to dissolve the precipitate. The biphasic solution was separated and the organic phase was washed with water (3 x 50 mL). The combined aqueous phase was washed with ether (1 x 50 mL). The combined organic extracts were dried, filtered and the solvent removed *in vacuo* to yield the crude *oxadiazoline* (2.08 g, 83%) as a pale yellow solid. δ_H: 2.43 (3H, s, ArC$\underline{H}_3$), 2.56 [2H, m, N(C$\underline{H}_{ax}$)$_2$], 2.68 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.62 [4H, t, J = 4.77, O(C$\underline{H}_2$)$_2$], 6.15 (1H, s, NC$\underline{H}$ON), 7.32 (7H, m, Ar$\underline{H}$), 7.67 (2H, m, Ar$\underline{H}$); m/z = 191, M^+ *N*-(*N´*-phenylformimidoyl)-morpholine (**341**).

Method 2: NMR spectroscopy tube reaction

1-*p*-Toluenesulfonyl-1-bromoformaldoxime (19.50 mg, 0.07 mmol) combined with 0.07 M triethylamine solution (1 mL, $CDCl_3$) and 0.6 mL of solution transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out. δ_H: 2.50 (3.15H, m, ArC$\underline{H}_3$ **309** & **307**), 7.18 (0.16H, m, Ar$\underline{H}$ **307** & **309**), 7.44 (1.36H, m, Ar$\underline{H}$ **307** & **309**), 7.51 (0.18H, m, Ar$\underline{H}$ **307** & **309**), 7.76 (0.21H, m, Ar$\underline{H}$ **307** & **309**), 7.88 (0.48H, m, Ar$\underline{H}$ **307** & **309**), 7.96 (0.17H, m, Ar$\underline{H}$ **307** & **309**), 8.03 (1H, m, Ar$\underline{H}$ **307** & **309**). The NMR spectroscopy tube contents were combined with the remainder of the original sample and then in turn combined with *N*-(*N´*-phenylformimidoyl)-morpholine (13.60 mg, 0.07 mmol). The solution was mixed briskly and a 0.6 mL portion was transferred to and NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out. δ_H: 2.50 (2.40H, m, 2 x ArC$\underline{H}_3$ **309**), 3.54 [4H, bs, N(C$\underline{H}_2$)$_2$ **341**], 3.75 [4.22H, m, O(C$\underline{H}_2$)$_2$ **341**], 6.98 (2H, m, Ar$\underline{H}$ **341**), 7.03 (1H, m, Ar$\underline{H}$ **341**), 7.18 (0.225H, m, Ar$\underline{H}$ **309**), 7.27 (2.35H, m, Ar$\underline{H}$ **309** & **341**), 7.44 (1.383H, m, Ar$\underline{H}$ **309**), 7.51 (0.16H, m, **309**), 7.56 (1H, s, C$\underline{H}$=N **341**), 7.76 (0.238H, m, **309**), 7.88 (0.43H, m, **309**), 7.96 (0.167H, m, **309**), 8.03 (0.954H, m, **309**).

Ratio of 3,4-*bis*-(*p*-toluenesulfonyl)-furoxan (**309**) : *N*-(*N´*-phenylformimidoyl)-morpholine (**341**) (29 : 71).

Method 3

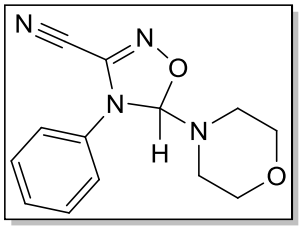
A solution of 1-*p*-toluenesulfonyl-1-bromoformaldoxime (0.90 g, 3.25 mmol) in ether (10 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (0.62 g, 3.25 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). Following addition, the solution was warmed to room temperature and stirred for 1 h. The solution was filtered and the solvent was removed *in vacuo* (without heat) to yield crude *oxadiazoline* as a yellow oil, (0.705 g). The residue was dissolved in chloroform and hexane was added. The solution was placed in a freezer and a mixture containing the *oxadiazoline* (55 mg, 4%) was isolated by vacuum filtration as an orange solid. δ_H: 2.43 (3.45H, s, ArC$\underline{H}_3$ **401**), 2.55 [2H, m, N(C$\underline{H}_{ax}$)$_2$ **401**], 2.67 [2H, m, N(C$\underline{H}_{eq}$)$_2$ **401**], 3.54 [4.9H, m, N(C$\underline{H}_2$)$_2$ **341**], 3.61 [4.9H, m, O(C$\underline{H}_2$)$_2$ **401**], 3.72 [7.27H, m, O(C$\underline{H}_2$)$_2$ **341**], 6.14 (1H, s, NC$\underline{H}$ON **401**), 7.03 (5.25H, m, Ar$\underline{H}$ **341**), 7.26 (8H, m, Ar$\underline{H}$ **341** & **401**), 7.36 (3.8H, m, Ar$\underline{H}$ **401**), 7.60 (1.8H, s, N=C$\underline{H}$ **341**), 7.65 (2H, m, Ar$\underline{H}$ **401**). Ratio oxadiazoline (**401**) : *N*-(*N´*-phenylformimidoyl)-morpholine (**341**) (36 : 64). m/z = 191, $(M+H)^+$ *N*-(*N´*-phenylformimidoyl)-morpholine (**341**).

Method 4

A solution of 1-*p*-toluenesulfonyl-1-bromoformaldoxime (0.90 g, 3.25 mmol) in ether (20 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (0.62 g, 3.25 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). The pale yellow cloudy mixture which resulted was warmed to room temperature and stirred for 32 min. The solution was filtered and the solvent was removed *in vacuo* (without heat). The residue was recrystallised from cold ethyl acetate:hexane and a mixture containing the *oxadiazoline* (528.00 mg, 42%) was isolated by vacuum filtration as a pale yellow solid, m.p. 70-72 ^{o}C, ν_{max} (KBr): 3067, 2966, 2916, 1734, 1595, 1553, 1496, 1376, 1327, 1154, 1116, 1039 cm^{-1}; δ_H: 2.46 (3H, s, PhC$\underline{H}_3$), 2.58 [2H, m, N(C$\underline{H}_{ax}$)$_2$], 2.71 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.64 [4H, t, J = 4.78, O(C$\underline{H}_2$)$_2$], 6.16 (1H, s, NC$\underline{H}$ON), 7.35 (7H, m, Ar$\underline{H}$), 7.69 (2H, m, Ar$\underline{H}$); δ_C: 21.9 (Ar$\underline{C}$H$_3$), 44.7 [N($\underline{C}$H$_2$)$_2$], 66.6 [O($\underline{C}$H$_2$)$_2$], 111.1 (N$\underline{C}$HON), 126.3, 128.1, 129.2, 129.3 and

129.9 (5 x ArCH), 129.4 [*p*-ArC(CH$_3$)], 135.1 and 136.6 (2 x *ipso* C of Ar), 146.4 (C=N). m/z = 388 $(M+H)^+$ **401**.

8.1.3.11 3-Cyano-4-phenyl-5-(4'-morpholino)-Δ²-1,2,4-oxadiazoline 402

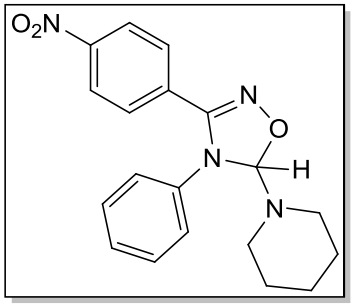


A solution of cyanoformohydroximoyl chloride (0.21 g, 2.00 mmol) in ether (6 ml) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10^{o}C, water/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-morpholine (0.38 g, 2.00 mmol) and triethylamine (0.28 ml, 2.01 mmol) in ether (11 mL). The resulting orange cloudy mixture was warmed to room temperature and stirred for 10 min. The mixture was filtered to remove the precipitate and the solvent was evaporated *in vacuo* (without heat) to yield the crude oxadiazoline as a pale orange oil. Recrystallisation from cold ether-hexane afforded a mixture of the oxadiazoline and amidine as a yellow solid. m.p. 59-63 ^{o}C. ν_{max} (film): 3059, 2964, 2916, 2855, 2248 (weak), 1694, 1630, 1587, 1550, 1500, 1421, 1164, 1115cm^{-1}; δ_H: 2.76 [2H, m, N(CH$_{ax}$)$_2$], 2.89 [2H, m, N(CH$_{eq}$)$_2$], 3.52 (4H, bs, N(CH$_2$)$_2$ **341**), 3.74 [8H, m, O(CH$_2$)$_2$ **402** and **341**], 6.38 (1H, s, NCHON), 6.96 (1.86H, m, ArH **341**), 7.03 (1H, m, ArH **341**), 7.30 (5.88H, m, ArH inc. 2H, m, **341**), 7.43 (2.16H, m, ArH **341**), 7.52 (1.1H, s, N=CH **341**); δ_C: 44.79 [N(CH$_2$)$_2$], 45.98 [N(CH$_2$)$_2$ **341**], 66.49 [O(CH$_2$)$_2$], 66.70 [O(CH$_2$)$_2$ **341**], 107.55 (CN), 108.83 (NCHON), 121.09, 122.92 and 129.05 (3 x ArCH **341**), 121.58 and 129.84 (2 x ArCH), 127.01 (*p*-ArCH), 132.17 (*ipso* C of Ar **341**), 135.7 (*ipso* C of Ar), 151.45 (C=N), 152.3 (N=CH **341**). HRMS (ESI^+) exact mass calculated for $C_{13}H_{14}N_4O_2$ [$(M+H)^+$], 259.1195, found 259.1189.

8.1.4 Reactions of *N*-phenylformimidoylpiperidine with *p*-nitrobenzohydroximoyl chloride

8.1.4.1 Attempted preparation of 3-(*p*-nitrophenyl)-4-phenyl-5-piperidino-Δ²-1,2,4-oxadiazoline 404

Method 1



A solution of *p*-nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) in ether (10 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/ice bath), stirring solution of *N*-(*N´*-

phenylformimidoyl)-piperidine (0.61 g, 3.25 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). The resulting cloudy mixture was warmed to room temperature and stirred for 10 min. The mixture was filtered with the aid of ether (10 mL) and the solvent was evaporated *in vacuo* (without heat) to yield a bright yellow solid/oil, (0.71 g, 62%). An attempt at crystallisation on the compound from chloroform and hexane was unsuccessful at room temperature so the mixture was transferred to a freezer. The recrystallised *oxadiazoline* (84.00 mg, 7%) was isolated by vacuum filtration as a yellow solid. The compound was dried under high vacuum, but had decomposed prior to full characterization being carried out. Decomposition products purified by column chromatography: Gradient eluent used, Ethyl acetate:hexane (10-80%).

F14-20: pale yellow solid isolated, 9 mg, δ_H: 3.48 (5H, m, piperidine ring), 3.74 (5H, m, piperidine ring), 6.37 (1H, bs, NH), 7.07 (1H, m, ArH), 7.34 (4H, m, ArH). MS = no diagnostic molecular ions.

F26-28: yellow solid isolated, 5.6 mg, δ_H: 8.01 (2H, d, J = 8.95, ArH), 8.32 (2H, d, J = 8.94, ArH). m/z = no diagnostic molecular ions.

Method 2

A solution of *p*-nitrobenzohydroximoyl chloride (1.00 g, 5.00 mmol) in ether (15.5 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^oC, water/ice bath), stirring solution of *N*-(*N´*-phenylformimidoyl)-piperidine (0.94 g, 5.00 mmol) and triethylamine (0.7 mL, 5.02 mmol) in ether (23 mL). The resulting yellow cloudy mixture was warmed to room temperature and stirred for 1 h. The mixture was filtered and the solution was evaporated *in vacuo* (without heat) to yield a pale yellow solid. δ_H: 1.57 (9.64H, m, CH_2 **404** & **337**], 1.83 [3.10H, m, CH_2 **404**], 2.72 [2.03H, m, CH_2 **404**], 2.93 [1.97H, m, CH_2 **404**], 3.12 [2.20H, m, CH_2 **404**], 3.50 [1.75H, m, CH_2 **337**], 6.20 (1H, s, NCHON **404**), 6.45 (0.40H, bs, NH **337**), 7.03 (2.40H, m, ArH **404** & **337**), 7.18 (1.54H, m, ArH **404**), 7.26 (3.54H, m, ArH **404** & **337**), 7.38 (2.18H, m, ArH **404** & **337**), 7.54 (1.30H, m, ArH **404**), 7.71 (2.89H, m, ArH **404** & **265**), 7.90 (1.92H, m, ArH **337**), 8.02 (1.73H, m, ArH **404**), 8.21 (4.33H, m, ArH **404**), 8.31 (1.54H, m, ArH **265**), 8.37 (1.86H, m, ArH **378**). The compound was recrystallised from ethyl acetate: cold distilled hexane and recrystallisation was aided by placing the solution in a freezer overnight. A mixture was isolated by vacuum filtration as a yellow solid (131.00 mg, 7%).

The recrystallisation product showed a mixture of *p*-nitrobenzonitrile (**378**) and *N*-phenyl-1-piperidine carboxamide (**337**) only, the oxadiazoline (**404**) was not isolated.

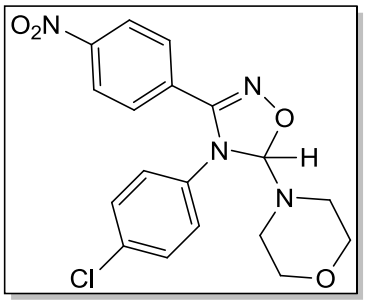
Method 3: NMR spectroscopy tube reaction

0.07 M Triethylamine solution (1 mL, $CDCl_3$) was added to a sample vial containing *p*-nitrobenzohydroximoyl chloride (14.00 mg, 0.07 mmol) and the solution mixed. A 0.7 mL portion of this solution was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out. Once complete, the mixture was recombined with the remaining solution and the entire contents were transferred to a sample vial containing *N*-(*N´*-phenylformimidoyl)-piperidine (13.20 mg, 0.07 mmol) and solution mixed briskly until homogenous and a 0.7 mL portion of this solution was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out immediately. The ^{1}H NMR spectrum obtained immediately after the addition of amidine to nitrile oxide showed that the oxadiazoline formed. Subsequent ^{1}H NMR spectroscopic data illustrates that decomposition had occurred 20 h later.

8.1.5 Reactions of *N*-*p*-chlorophenylformimidoylmorpholine with *p*-nitrobenzohydroximoyl chloride

8.1.5.1 3-(*p*-Nitrophenyl)-4-(*p*-chlorophenyl)-5-(*N*-morpholino)-Δ^2-1,2,4-oxadiazoline 405

Method 1



p-Nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) in ether (10 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-*p*-chlorophenylformimidoyl)-morpholine (0.73 g, 3.25 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). The resulting solution was warmed to room temperature and stirred for 10 min. The solution was filtered and the solvent was removed *in vacuo* (without heat) to yield a yellow solid with a yellow liquid, (0.35 g). An attempt to crystallise the compound from chloroform:hexane was unsuccessful, so the compound was placed in a freezer. The *oxadiazoline* (41.00 mg, 3%) was isolated by vacuum filtration as a pale yellow crystalline solid, m.p. 123-147 ^{o}C, (Found: C, 54.74; H, 4.41; N, 14.09 $C_{18}H_{17}ClN_4O_4$ requires C, 55.60; H,4.41; N,14.41%), ν_{max} (KBr): 3072,

1582, 1566, 1519, 1489, 1349, 1256, 1120, 786 cm^{-1}; δ_H : 2.78 [2H, m, N(C<u>H</u>$_{ax}$)$_2$], 2.95 [2H, m, N(C<u>H</u>$_{eq}$)$_2$], 3.79 [4H, t, J = 4.62, O(C<u>H</u>$_2$)$_2$], 6.15 (1H, s, NC<u>H</u>ON), 6.99 (2H, d, J = 8.52, *m*-Ar<u>H</u> on C_3), 7.24 (2H, d, J = 8.46, *o*-Ar<u>H</u> on C_3), 7.68 (2H, d, J = 8.58, *m*-Ar<u>H</u> on N_4), 8.20 (2H, d, J = 8.58, *o*-Ar<u>H</u> on N_4); δ_C: 44.98 [N(<u>C</u>H$_2$)$_2$], 66.80 [O(<u>C</u>H$_2$)$_2$], 109.32 (N<u>C</u>HON), 124.07 (*o*-Ar<u>C</u>H on C_3), 124.36 (*m*-Ar<u>C</u>H on N_4), 128.52 (*m*-Ar<u>C</u>H on C_3), 129.55 (*o*-Ar<u>C</u>H on N_4), 131.14 [*p*-Ar<u>C</u>(NO$_2$)], 131.78 [*p*-Ar<u>C</u>(Cl)], 148.86 (*ipso* <u>C</u> of Ar on C_3), 151.49 (<u>C</u>$_3$ of oxadiazoline ring). m/z = 389 $(M+H)^+$; HRMS (ESI^+) exact mass calculated for $C_{18}H_{17}N_4O_4Cl$ $[M+H]^+$ 389.1017, found 389.1003.

Method 2

p-Nitrobenzohydroximoyl chloride (1.30 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-(*N´-p*-chlorophenylformimidoyl)-morpholine (1.46 g, 6.50 mmol) and triethylamine (0.91 mL, 6.53 mmol) in ether (30 mL). Following addition, the solution was warmed to room temperature and stirred for 2 h 10 min. The mixture was filtered to remove the precipitate and the solvent was removed *in vacuo* to yield an orange oil. The *oxadiazoline* (0.10 g, 4%) was recrystallised from chloroform:hexane and isolated by vacuum filtration as an orange crystalline solid. δ_H: 2.78 [2H, m, N(C<u>H</u>$_{ax}$)$_2$], 2.95 [2H, m, N(C<u>H</u>$_{eq}$)$_2$], 3.79 [4H, t, J = 4.75, O(C<u>H</u>$_2$)$_2$], 6.15 (1H, s, NC<u>H</u>ON), 6.99 (2H, m, Ar<u>H</u>), 7.24 (2H, m, Ar<u>H</u>), 7.68 (2H, m, Ar<u>H</u>), 8.20 (2H, m, Ar<u>H</u>). m/z = 241 $(M+H)^+$ 4-(4-chlorophenylcarbamoyl)-morpholine (**434**), 225 $(M+H)^+$ *N*-(*N´-p*-chlorophenylformimidoyl)-morpholine (**345**).

Method 3: NMR spectroscopy tube reaction

Triethylamine solution (1 mL, 0.07 M solution in $CDCl_3$) was added to *p*-nitrobenzohydroximoyl chloride (14.00 mg, 0.07 mmol) and the solution was briskly mixed and a 0.6 mL portion was transferred to an NMR spectroscopy tube and ^1H NMR spectroscopic analysis carried out immediately. The contents of the NMR spectroscopy tube were combined with the remaining 0.4 mL of solution and the entire (1 mL) of solution was transferred to sample vial containing *N*-(*N´-p*-chlorophenylformimidoyl)-morpholine (15.70 mg, 0.07 mmol). This solution was mixed briskly and a 0.6 mL portion was transferred to an NMR spectroscopy tube and ^1H NMR spectroscopic analysis was carried out immediately. Exp 11 took place 9 min after nitrile oxide check: δ_H: 2.78 [2H, bm, N(C<u>H</u>$_{ax}$)$_2$ **405**], 2.95 [2H, bm, O(C<u>H</u>$_{eq}$)$_2$ **405**], 3.51 [1.26H, bs, N(C<u>H</u>$_2$)$_2$ **345**], 3.75

[1.58H, m, O(C<u>H</u>$_2$)$_2$ **345**], 3.80 [4H, t, J = 4.73, O(C<u>H</u>$_2$)$_2$ **405**], 6.16 (1H, s, NC<u>H</u>ON **405**), 6.89 (0.65H, m, Ar<u>H</u> **345**), 6.99 (2H, m, Ar<u>H</u> **405**), 7.24 (3H, m, Ar<u>H</u> **405** & **345**), 7.51 (0.41H, s, N=C<u>H</u> **345**), 7.71 (2.48H, m, Ar<u>H</u> **405**, **265** & **345**), 8.21 (2H, m, Ar<u>H</u> **405**), 8.30 (0.61H, m, Ar<u>H</u> **265**).

Exp 12 took place 1 h 6 min after exp 11: δ_H: 2.78 [2H, bm, N(C<u>H</u>$_{ax}$)$_2$ **405**], 2.95 [2.11H, m, N(C<u>H</u>$_{eq}$)$_2$ **405**], 3.51 [0.50H, bs, N(C<u>H</u>$_2$)$_2$ **345**], 3.75 [0.75H, m, O(C<u>H</u>$_2$)$_2$ **345**], 3.83 [3.91H, t, J = 4.73, O(C<u>H</u>$_2$)$_2$ **405**], 6.16 (1H, s, NC<u>H</u>ON **405**), 6.88 (0.25H, m, Ar<u>H</u> **345**), 6.99 (2H, m, Ar<u>H</u> **405**), 7.24 (2.55H, m, Ar<u>H</u> **405** & **345**), 7.51 (0.17H, s, N=C<u>H</u> **345**), 7.69 (2H, m, Ar<u>H</u> **405**), 8.21 (2H, m, Ar<u>H</u> **405**).

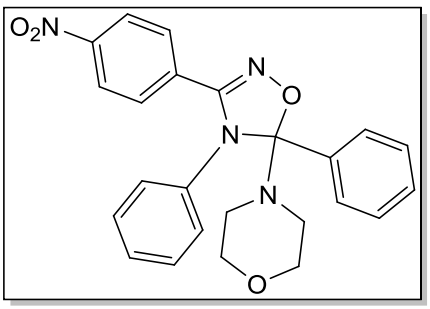
Exp 13 took place 4 h 36 min after exp 11: δ_H: 2.78 [2H, bm, N(C<u>H</u>$_{ax}$)$_2$ **405**], 2.95 [2.11H, m, N(C<u>H</u>$_{eq}$)$_2$ **405**], 3.51 [0.50H, bs, N(C<u>H</u>$_2$)$_2$ **345**], 3.74 [0.68H, m, O(C<u>H</u>$_2$)$_2$ **345**], 3.80 [4H, t, J = 4.73, O(C<u>H</u>$_2$)$_2$ **405**], 6.16 (1H, s, NC<u>H</u>ON **405**), 6.88 (0.25H, m, Ar<u>H</u> **345**), 6.99 (2H, m, Ar<u>H</u> **405**), 7.24 (2.54H, m, Ar<u>H</u> **405** & **345**), 7.51 (0.15H, s, N=C<u>H</u> **345**), 7.69 (2H, m, Ar<u>H</u> **405**), 8.20 (2.19H, m, Ar<u>H</u> **405**).

8.2 1,3-Dipolar cycloaddition reactions with benzamidines

8.2.1 Reactions with *N*-(*N´*-phenylbenzimidoyl)-morpholine

8.2.1.1 3-(*p*-Nitrophenyl)-4-phenyl-5-phenyl-5'-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 406

Method 1



A solution of *p*-nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) in ether (10 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-phenylbenzimidoyl)-morpholine (0.87 g, 3.25 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). Following addition, the solution was warmed to room temperature and stirred for 1 h. The resulting solution was filtered and the solvent was removed *in vacuo* (without heat) to yield the crude oxadiazoline as a pale orange solid (0.266 g). This sample was recrystallised from chloroform:hexane and the resulting solution was placed in a freezer to aid crystallisation. The *oxadiazoline* (96.00 mg, 7%) was isolated by vacuum filtration as a

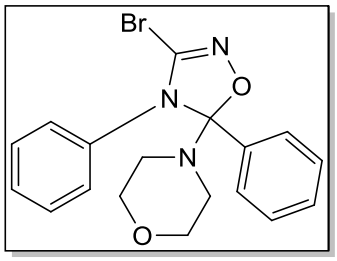
bright yellow crystalline solid, m.p. 180-181 ^{o}C, (Found: C, 63.60; H, 4.94; N, 10.94 $C_{24}H_{22}N_4O_4$ requires C, 66.97; H, 5.15; N, 13.02 %), ν_{max} (KBr): 3064, 1598, 1572, 1522, 1494, 1350 cm^{-1}; δ_H: 2.85 [2H, m, N(C$\underline{H}_{ax}$)$_2$], 3.17 [2H, m, N(C$\underline{H}_{eq}$)$_2$], 3.86 [4H, m, O(C$\underline{H}_2$)$_2$], 6.73 (2H, m, *o*-Ar$\underline{H}$ on C_5), 7.07 (3H, m, *m*-Ar$\underline{H}$ and *p*-Ar$\underline{H}$ on C_5), 7.15 (3H, m, *m*-Ar$\underline{H}$ and *p*-Ar$\underline{H}$ on N_4), 7.38 (2H, m, *o*-Ar$\underline{H}$ on N_4), 7.56 (2H, m, *o*-Ar$\underline{H}$ on C_3), 8.08 (2H, m, *m*-Ar$\underline{H}$ on C_3); δ_C: 45.87 [N($\underline{C}$H$_2$)$_2$], 67.01 [O($\underline{C}$H$_2$)$_2$], 115.09 ($\underline{C}_5$ of oxadiazoline ring), 123.59 (*m*-Ar$\underline{C}$H at C_3), 127.16 (*p*-Ar$\underline{C}$H at C_5), 127.58 (*o*-Ar$\underline{C}$H at C_5), 127.73 (*o*-Ar$\underline{C}$H at N_4), 127.89 (*p*-Ar$\underline{C}$H on N_4), 128.72 (*o*-Ar$\underline{C}$H on C_3), 128.95 (*p*-Ar$\underline{C}$H at N_4 and *m*-Ar$\underline{C}$H at C_5), 131.97 [Ar$\underline{C}$(NO$_2$)], 135.11 (*ipso* $\underline{C}$ of Ar at N_4), 136.94 (*ipso* $\underline{C}$ of Ar at C_5), 148.43 (*ipso* $\underline{C}$ of Ar at C_3), 151.64 ($\underline{C}_3$ of oxadiazoline ring). m/z = [O_6010] 431 (M+H)$^+$; HRMS (ESI$^+$) exact mass calculated for $C_{24}H_{22}N_4O_4$ [M+H]$^+$ 431.1719, found 431.1722.

Method 2: NMR spectroscopy tube reaction

1 mL of 0.07 M triethylamine solution in $CDCl_3$ was added to solid *p*-nitrobenzohydroximoyl chloride (14.10 mg, 0.07 mmol) and a 0.6 mL portion of this solution was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out. The NMR spectroscopy tube contents were returned to the sample vial and were combined with *N*-(*N´*-phenylbenzimidoyl)-morpholine (**349**) (18.90 mg, 0.07 mmol). A 0.6 mL portion of this solution was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out. This sample was monitored over time by ^{1}H NMR spectroscopy. δ_H: 2.85 [2H, m, N(C$\underline{H}_{ax}$)$_2$ **406**], 3.17 [2H, m, N(C$\underline{H}_{eq}$)$_2$ **406**], 3.41 [0.73H, bs, N(C$\underline{H}_2$)$_2$ **349**], 3.74 [0.88H, m, O(C$\underline{H}_2$)$_2$ **349**], 3.86 [4H, m, O(C$\underline{H}_2$)$_2$ **406**], 6.56 (2H, m, Ar$\underline{H}$ **349**) 6.72 (2.1H, m, Ar$\underline{H}$ **406** & **349**), 7.00 (0.4H, m, Ar$\underline{H}$ **349**), 7.09 (3H, m, Ar$\underline{H}$ **406**), 7.14 (3.17H, m, Ar$\underline{H}$ **406** & **349**), 7.23 (0.67H, m, Ar$\underline{H}$ **349**), 7.38 (2H, m, Ar$\underline{H}$ **406**), 7.56 (2H, m, Ar$\underline{H}$ **406**), 8.09 (2.1H, m, Ar$\underline{H}$ **406** & **349**).

8.2.1.2 Attempted preparation of 3-bromo-4,5-*di*phenyl-5'-(4'-morpholino)-Δ^2-1,2,4-oxadiazoline 407

Method 1



Dibromoformaldoxime (0.20 g, 1.01 mmol) in ether (5 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N´*-phenylbenzimidoyl)-morpholine (0.27 g, 1.01 mmol) and triethylamine (0.11 g, 1.06 mmol) in ether (10 mL). The clear solution became yellow and then orange during addition. The solution was warmed to room temperature, stirred for 10 min and was filtered. The solvent was removed *in vacuo* (without heat) to yield an orange/brown oil with solid (0.233 g, 56%). ν_{max} (film): 3060, 2221, 1614, 1494, 1434, 1278, 1258, 1115, 1068, 1020 cm^{-1}; δ_H: 3.76 (8H, bm, N(C<u>H</u>$_2$)$_2$ and O(C<u>H</u>$_2$)$_2$ **322** & ?), 6.91 (1.89H, m, Ar<u>H</u>), 7.05 (2.05H, m, Ar<u>H</u>), 7.33 (7.16H, m, Ar<u>H</u> **322** & ?). m/z = 267 (100%, (M+H)$^+$ **349**), 192 (M+H)$^+$ **322**. The crude reaction product was purified by column chromatography on silica gel using ethyl acetate: hexane as eluents. Initially, 20 : 80 ethyl acetate : hexane used, which was gradually increased as separation continued to 60:40 ethyl acetate : hexane. Two separate fractions were isolated. The first of which correlated to a mixture of predominantly *N*-(*N´*-phenylbenzimidoyl)-morpholine (**349**) and a small quantity of *N*-benzoylmorpholine (**322**). This sample was analysed by ^{1}H NMR spectroscopy, δ_H: 3.42 (4.47H, bs, N(C<u>H</u>$_2$)$_2$ **349** & **322**), 3.75 (5.13H, bt, J = 4.70, O(C<u>H</u>$_2$)$_2$ **349** & **322**), 6.42 (0.31H, m, Ar<u>H</u>), 6.56 (1.92H, m, Ar<u>H</u> **349**), 6.75 (1H, m, Ar<u>H</u> **349**), 7.00 (2.14H, m, Ar<u>H</u> **349**), 7.12 (2.67H, m, Ar<u>H</u> **349**), 7.23 (3.29 H, m, Ar<u>H</u> **349**), 7.42 (1.87H, m, Ar<u>H</u> **322**). The ratio of *N*-(*N´*-phenylbenzimidoyl)-morpholine (**349**) : *N*-benzoylmorpholine (**322**) was 73 : 27. m/z = 347, 345, 267 (M+H)$^+$ 100% **349**. The second fraction which was analysed by ^{1}H NMR spectroscopy, δ_H: 3.59 [74.96H, bm, N(C<u>H</u>$_2$)$_2$ and O(C<u>H</u>$_2$)$_2$ **322** & **349**], 6.42 (0.60H, m, Ar<u>H</u>), 6.56 (1.88H, m, Ar<u>H</u> **349**), 6.75 (1H, m, Ar<u>H</u> **349**), 7.00 (2.07H, m, Ar<u>H</u> **349**), 7.11 (3.40H, m, Ar<u>H</u> **349**), 7.23 (3.50H, m, Ar<u>H</u> **349**), 7.41 (33.36H, m, Ar<u>H</u> **322**). The ratio of *N*-(*N´*-phenylbenzimidoyl)-morpholine (**349**) : *N*-benzoylmorpholine (**322**) was 13 : 87. m/z = 383 (2M+H)$^+$ *N*-benzoylmorpholine (**322**), 347, 345, 267 (M+H)$^+$ (100%) *N*-(*N´*-phenylbenzimidoyl)-morpholine (**349**).

Method 2

Dibromoformaldoxime (0.21 g, 1.03 mmol) in ether (5 mL) was added dropwise *via* Pasteur pipette to a cooled (<10 ^{o}C, water/icebath), stirring suspension of *N*-(*N´*-phenylbenzimidoyl)-morpholine (0.27 g, 0.99 mmol) and potassium *t*-butoxide (0.12 g, 1.03 mmol) in ether (10 mL). The mixture became orange in colour during addition. The mixture was warmed to room temperature, stirred for 10 min and filtered. The solvent was removed *in vacuo* (without heat). An orange solid residue and pale brown oily residue resulted (0.2388 g), ν_{max} (film): 3061, 2238, 1614, 1488, 1434, 1276, 1115 cm^{-1}; δ_H: 3.79 [10.44H, bm, N(C$\underline{H}_2$)$_2$ and O(C$\underline{H}_2$)$_2$ **322** & ?], 6.94 (0.34H, m, Ar$\underline{H}$), 7.10 (4,25H, m, Ar$\underline{H}$), 7.31 (2.51H, m, Ar$\underline{H}$), 7.37 (1.26H, m, Ar$\underline{H}$), 7.41 (5H, m, Ar$\underline{H}$ 322). m/z = 192 [M+H]$^+$ **322**. The crude reaction product was purified by column chromatography on silica gel using ethyl acetate and hexane as eluents. Initially, 10:90 ethyl acetate : hexane used, which was gradually increased as separation continued to 100% ethyl acetate. The fractions correlating to *N*-benzoylmorpholine (**322**) (F25-32) were combined. ν_{max} (film): 3059, 1629, 1431, 1278, 1259, 1114 cm^{-1}; δ_H: 3.59 [8H, m, N(C$\underline{H}_2$)$_2$ and O(C$\underline{H}_2$)$_2$], 7.50 (5H, m, Ar$\underline{H}$); δ_C: 42.5 [N(C$\underline{H}_2$)$_2$], 66.9 [O(C$\underline{H}_2$)$_2$], 127.1, 128.6 and 129.9 (3 x Ar$\underline{C}$H), 135.4 (*ipso* $\underline{C}$ of Ar), 170.4 ($\underline{C}$=O). m/z = 383 [(2M+H)$^+$ 100% *N*-benzoylmorpholine (**322**)].

Method 3

Dibromoformaldoxime (1.32 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N*'-phenylbenzimidoyl)-morpholine (1.73g, 6.50 mmol) and triethylamine (0.66 g, 6.51 mmol) in ether (30 mL). The solution was filtered and solvent removed *in vacuo* (without heat) (1.79 g, 71%). ν_{max} (film): 3060, 2221, 1621, 1589, 1445, 1434, 1278, 1257, 1114 cm^{-1}; δ_H: 3.65 [12.11H, bm, N(C$\underline{H}_2$)$_2$ and O(C$\underline{H}_2$)$_2$ **322** & ?], 6.75 (2H, m, Ar$\underline{H}$?), 6.85 (1.05H, m, Ar$\underline{H}$?), 6.91 (0.21H, m, Ar$\underline{H}$?), 7.03 (2.93H, m, Ar$\underline{H}$?), 7.18 (2.15H, m, Ar$\underline{H}$?), 7.28 (4.08H, m, Ar$\underline{H}$?), 7.36 (0.34H, m, Ar$\underline{H}$?), 7.42 (3.29H, m, Ar$\underline{H}$ **322**). m/z = 383 [(2M+H)$^+$ *N*-benzoylmorpholine (**322**)]

Method 4

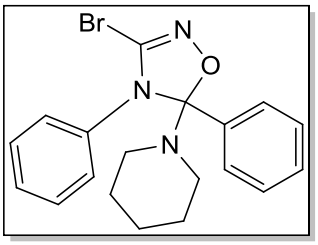
Dibromoformaldoxime (1.32 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring suspension

of *N*-(*N*'-phenylbenzimidoyl)-morpholine (1.74 g, 6.51 mmol) and potassium *t*-butoxide (0.73 g, 6.51 mmol) in ether (30 mL). The mixture was filtered and the solvent was removed *in vacuo* (without heat) (1.88 g, 74%). ν_{max} (film): 3061, 2237, 1614, 1494, 1445, 1276, 1116 cm^{-1}; δ_H: 3.72 [11.10H, bm, N(C<u>H</u>$_2$)$_2$ and O(C<u>H</u>$_2$)$_2$ **322** & ?], 7.05 (5.39H, m, Ar<u>H</u> ?), 7.31 (4.72H, m, Ar<u>H</u> ?), 7.41 (5H, m, Ar<u>H</u> **322**); m/z = 383 [$(2M+H)^+$, *N*-benzoylmorpholine (**322**)].

8.2.2 Reactions with *N*-(*N*'-phenylbenzimidoyl)-piperidine

8.2.2.1 Attempted preparation of 3-bromo-4,5-*di*phenyl-5'-(*N*-piperidino)-Δ^2-1,2,4-oxadiazoline 416

Method 1



Dibromoformaldoxime (1.32 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-(*N*'-phenylbenzimidoyl)-piperidine (1.73 g, 6.54 mmol) and triethylamine (0.66 g, 6.50 mmol) in ether (30 mL). The solution was warmed to room temperature and stirred for ten min. The cloudy mixture was filtered and the solvent was removed *in vacuo* (without heat) to yield a brown oil (0.48 g, 19%). ν_{max} (film): 3060, 2220, 1614, 1495, 1445, 1277 cm^{-1}. ^{1}H NMR spectroscopicc analysis indicated that *N*-benzoylpiperidine (**324**) was isolated. δ_H: 1.52 (2.03H, bs, C<u>H</u>$_2$ **324**), 1.68 (3.89H, bs, C<u>H</u>$_2$ **324** & ?), 1.79 (1.73H, bs, ?), 3.35(1.91H, bs, C<u>H</u>$_2$ **324**), 3.72 (1.97H, bs, C<u>H</u>$_2$ **324**), 6.91 (0.28H, m, Ar<u>H</u> ?), 7.04 (2.77H, m, Ar<u>H</u> ?), 7.31 (2.99H, m, Ar<u>H</u> ?), 7.40 (5H, m, Ar<u>H</u> **324**); m/z = 265 $(M+H)^+$ 100%, *N*-(*N*'-phenylbenzimidoyl)-piperidine (**350**).

Method 2

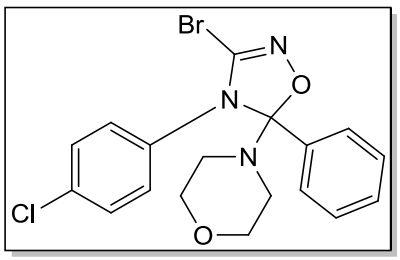
Dibromoformaldoxime (1.3 g, 6.48 mmol) in ether (20 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring suspension of *N*-(*N*'-phenylbenzimidoyl)-piperidine (1.73 g, 6.53 mmol) and potassium *t*-butoxide (0.73 g, 6.50 mmol) in ether (30 mL). On completion of addition, the brown/orange cloudy mixture was warmed to room temperature, stirred for ten min and was filtered. The solvent was removed *in vacuo* (without heat) to yield a brown oil (0.46 g, 18%). ν_{max} (film): 3060, 2238, 1614, 1495, 1445, 1277, 1245 cm^{-1}. ^{1}H NMR spectroscopicc analysis indicated that

N-benzoylpiperidine (**324**) was isolated. δ_H: 1.52 (2.35H, bs, C<u>H</u>$_2$ **324**), 1.68 (3.96H, C<u>H</u>$_2$ **324** & ?), 1.79 (1.33H, bs, ?), 3.34 (1.96H, bs, C<u>H</u>$_2$ **324**), 6.90 (0.36H, m, Ar<u>H</u> ?), 7.04 (2.79H, m, Ar<u>H</u> ?), 7.30 (1.38H, m, Ar<u>H</u> ?), 7.38 (5H, m, Ar<u>H</u> **324**); m/z = 265 $(M+H)^+$ (100%) *N*-(*N*'-phenylbenzimidoyl)-piperidine (**350**).

8.2.3 Reactions with *N*-(*p*-chlorophenyl)-benzimidoylmorpholine

8.2.3.1 Attempted preparation of 3-bromo-4-(*p*-chlorophenyl)-5-phenyl-5'-(*N*-morpholino)-Δ²-1,2,4-oxadiazoline 417

Method 1



Dibromoformaldoxime (1.32 g, 6.52 mmol) in ether (20 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-(*N*'-*p*-chlorophenyl)-benzimidoylmorpholine (1.96 g, 6.5 mmol) and triethylamine (0.66 g, 6.50 mmol) in ether (30 mL). On completion of addition, the solution was warmed to room temperature and stirred for ten min. The cloudy mixture was filtered and the solvent was removed *in vacuo* (without heat) (2.10 g, 76%), ν_{max} (film): 3060, 2236, 1621, 1492, 1280, 1254, 1114 cm^{-1}. ^1H NMR spectroscopicc analysis indicated that *N*-benzoylmorpholine (**322**) was isolated. δ_H: 3.65 (19.28H, m, Ar<u>H</u> **322** & ?), 6.71 (3.93H, m, Ar<u>H</u>), 6.98 (4.63H, m, Ar<u>H</u>), 7.21 (4.81H, m, Ar<u>H</u>), 7.33 (6.01H, m, Ar<u>H</u>), 7.42 (5H, m, Ar<u>H</u> **322**). m/z = 301 $(M+H)^+$, 100% *N*-(*N*'-*p*-chlorophenyl)-benzimidoylmorpholine (**353**).

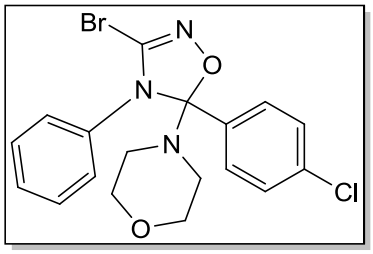
Method 2

Dibromoformaldoxime (1.32 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring suspension of *N*-(*N*'-*p*-chlorophenyl)-benzimidoylmorpholine (1.96 g, 6.51 mmol) and potassium *t*-butoxide (0.73 g, 6.50 mmol) in ether (30 mL). On completion of addition, the mixture was warmed to room temperature, stirred for ten min and was filtered. The solvent was removed *in vacuo* (without heat) (1.47 g, 53%). ν_{max} (film): 3061, 2237, 1615, 1492, 1363, 1301, 1279, 1177 cm^{-1}. ^1H NMR spectroscopicc analysis indicated that *N*-benzoylmorpholine (**322**) was isolated δ_H: 3.74 [13.56H, bm, N(C<u>H</u>$_2$)$_2$ and O(C<u>H</u>$_2$)$_2$ **322** &

?], 6.86 (2H, m, ArH), 6.96 (0.79H, m, ArH), 7.03 (2.06H, m, ArH), 7.23 (2.81H, m, ArH), 7.38 (8.26H, m, ArH **322** & ?). m/z = 383 $(2M+H)^+$ **322**, 301 $(M+H)^+$ 100% **353**.

8.2.4 Reactions with *N*-phenyl-(*p*-chlorobenzimidoyl)-morpholine

8.2.4.1 Attempted preparation of 3-bromo-4-phenyl-5-(*p*-chlorophenyl)-5'-(*N*-morpholino)-Δ²-1,2,4-oxadiazoline 418

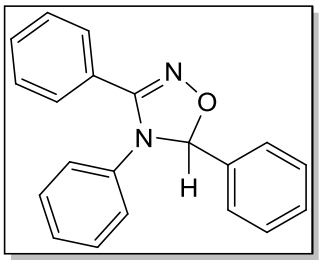


Dibromoformaldoxime (1.32 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 °C, water/icebath), stirring solution of *N*-phenyl-(*p*-chlorobenzimidoyl)-morpholine (1.96 g, 6.51 mmol) and triethylamine (0.67 g, 6.58 mmol) in ether (30 mL). A precipitate formed immediately. This precipitate was isolated by gravity filtration and the solvent evaporated *in vacuo* from the resulting filtrate (without heat). ν_{max} (film): 3060, 2238, 1614, 1114, 1011 cm^{-1}. ^1H NMR spectroscopicc analysis indicated that *N*-(p-chlorobenzoyl)-morpholine (**327**) was isolated δ_H: 3.45 (1.80H, bs), 3.72 [5.34H, bm, $N(CH_2)_2$ and $O(CH_2)_2$ **327** and ?], 4.28 (0.68H, bs), 6.95 (0.26H, m, ArH), 7.04 (0.60H, m, ArH), 7.15 (1.94H, m, ArH), 7.28 (0.57H, m, ArH), 7.38 (4H, m, ArH **327**).

8.3 1,3-Dipolar cycloaddition reactions with other dipolarophiles

8.3.1 1,3-Dipolar cycloaddition reactions with imines

8.3.1.1 3-Phenyl-4-phenyl-5-phenyl-Δ²-1,2,4-oxadiazoline 419

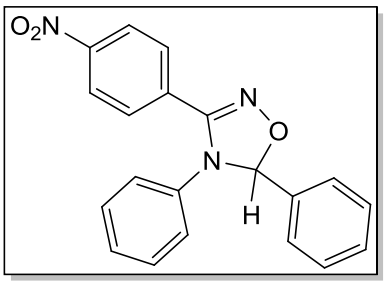


Benzohydroximoyl chloride (1.01 g, 6.52 mmol) in ether (20 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 °C, water/icebath), stirring solution of *N*-benzylideneaniline (1.18 g, 6.51 mmol) and triethylamine (0.66 g, 6.55 mmol) in ether (20 mL). The resulting mixture was warmed to room temperature and stirred overnight. The mixture was filtered to remove the precipitate. Additional ether (10 mL) was used to rinse the flask. The solvent was removed *in vacuo* (without heat) and any residual solvent was removed under high vacuum. A mixture of the crude *oxadiazoline* (1.74 g, 89%) and *N*-benzylideneaniline (**346**) was isolated as a pale orange liquid. (Lit. m.p. 76-77 °C)[219], ν_{max} (film): 3062, 3035, 1701, 1669, 1593, 1497, 1457, 1446, 1395 cm^{-1}; δ_H: 6.54 (1H, s, NCHON **419**), 6.79 (2H, m, ArH **419**), 7.16 (4.3H, m, ArH **419** & **346**), 7.35 (3.6H, m, ArH **419** & **346**), 7.45

(4.4H, ArH **419** & **346**), 7.61 (4.3H, m, ArH **419** & **346**), 7.91 (0.6H, m, ArH **346**), 8.46 (0.25H, m, N=CH **346**).

8.3.1.2 3-(*p*-Nitrophenyl)-4-phenyl-5-phenyl-Δ²-1,2,4-oxadiazoline 420

Method 1



p-Nitrobenzohydroximoyl chloride (1.31 g, 6.51 mmol) in ether (30 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 °C, water/icebath), stirring solution of *N*-benzylideneaniline (1.18 g, 6.50 mmol) and triethylamine (0.66 g, 6.52 mmol) in ether (40 mL). The mixture was warmed to room temperature and stirred for ten minutes. Water (30 mL) was added to dissolve the precipitate. The resulting biphasic solution was transferred to a separating funnel. As an emulsion was present, a further portion of ether (50 mL) was added to no avail. Water (120 mL) was then added. A slight dissipation of emulsion occurred. The phases were separated with the emulsion being transferred to aqueous phase. The organic layer was washed with water (2 x 30 mL). The combined aqueous phases were washed with distilled dichloromethane (50 mL). The dichloromethane layer was combined with the ether layer and the overall combined organic extracts were dried, filtered and solvent was evaporated *in vacuo*. Recrystallisation from ethyl acetate:hexane (2:5) yielded the *oxadiazoline* (1.34 g, 60%) as a green crystalline solid, m.p. 143-144 °C (Lit. m.p. 142-143 °C).[204] ν_{max} (KBr): 3082, 1597, 1562, 1514, 1494, 1413, 1340 cm^{-1}; δ_H: 6.55 (1H, s, NCHON), 6.81 (2H, m, ArH), 7.18 (3H, m, ArH), 7.46 (3H, m, ArH), 7.58 (2H, m, ArH), 7.77 [2H, m, *o*-ArH of *p*-NO_2(Ar)], 8.19 [2H, m, *m*-ArH of *p*-NO_2(Ar)]; δ_C: 101.4 (NCHON), 123.9, 124.6, 126.5, 127.2, 128.8, 128.9, 129.6 and 130.1 (8 x ArCH), 131.8 [ArC(NO_2)], 138.4 (*ipso* C of Ar at C_5 of oxadiazoline), 140.7 (*ipso* C of Ar at N_4 of oxadiazoline), 148.9 (*ipso* C of Ar at C_3 of oxadiazoline), 153.8 [NC(*p*-NO_2Ar)=N]; m/z = 346 $(M+H)^+$, 100%.

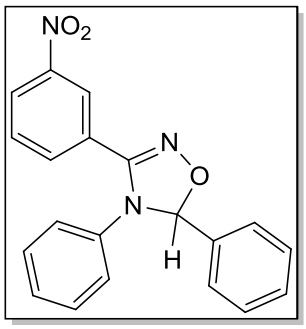
Method 2: NMR spectroscopy tube reaction

0.07 M Triethylamine solution (1 mL) was added to *p*-nitrobenzohydroximoyl chloride (14.50 mg, 0.07 mmol) and 0.6 mL was analysed by proton NMR spectroscopic analysis. The contents of the NMR spectroscopy tube were returned to the sample vial. The entire (1 mL) of solution was added to *N*-benzylidene aniline (12.70 mg, 0.07 mmol) and 0.6 mL of this solution was transferred to NMR spectroscopy tube and ^{1}H NMR spectroscopy used to

monitor the reaction. A mixture of products resulted and *N*-benzylidene aniline (**346**), *p*-nitrobenzonitrile-*N*-oxide (**265**) and oxadiazoline (**420**) were observed in a ratio of 42 : 38 : 20. δ_H: 6.55 (1H, s, NCHON **420**), 6.80 (2H, m, ArH **420**), 7.22 (10H, ArH **420** & **346**), 7.40 (4.8H, m, ArH **346**), 7.48 (9.6H, m, ArH **346** & **420**), 7.58 (2H, m, ArH **346**), 7.72 (4H, m, ArH **265**), 7.78 (2H, m, ArH **420**), 7.91 (4H, m, ArH **346**), 8.18 (2H, m, ArH **420**), 8.30 (4H, m, ArH **265**), 8.47 (2.2H, s, N=CH **346**).

8.3.1.3 3-(*m*-Nitrophenyl)-4-phenyl-5-phenyl-Δ^2-1,2,4-oxadiazoline 421

Method 1



m-Nitrobenzohydroximoyl chloride (1.31 g, 6.51 mmol) in ether (20 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-benzylideneaniline (1.18 g, 6.51 mmol) and triethylamine (0.66 g, 6.57 mmol) in ether (20 mL). A solid precipitated from the solution. On completion of addition, the solution was stirred overnight (16.25 h). The sample was filtered to remove the precipitate with the aid of ether (10 mL). The solvent was removed *in vacuo* and sample placed under high vacuum to remove any residual solvent. Recrystallisation from chloroform:hexane was unsuccessful and a mixture of products yielded a brown oil (0.89 g, 40%). A mixture of products resulted and *N*-benzylidene aniline (**346**) and oxadiazoline (**421**) were observed in a ratio of 22 : 78. ν_{max} (film): 3062, 1594, 1533, 1493, 1350 cm^{-1}; δ_H: 6.56 (1H, s, NCHON **421**), 6.83 (2H, m, ArH **421**), 7.19 (4H, m, ArH **421** & **346**), 7.39 (0.58H, m, ArH **346**), 7.46 (3.6H, m, ArH **421** & **346**), 7.53 (1.44H, t, J = 8.05, ArH **421**), 7.59 (2.21H, m, ArH **421**), 7.92 (1.63H, m, ArH **421** & **346**), 8.24 (1.14H, m, ArH **421**), 8.45 (1H, m, ArH **421**), 8.46 (0.28H, s, N=CH **346**).

Method 2

A solution of *m*-nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) in distilled dichloromethane (10 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-benzylideneaniline (0.59 g, 3.27 mmol) and triethylamine (0.46 mL, 3.30 mmol) in distilled dichloromethane (15 mL). The solution was warmed to room temperature and stirred for 10 min. Water (30 mL) was added and phases separated. Organic phase washed with water (1 x 20 mL). Organic phase dried, filtered and solvent evaporated *in vacuo* (without heat) to yield *oxadiazoline* (0.95 g,

85%) as a yellow liquid. ν_{max} (film): 3385, 3087, 3064, 1670, 1594, 1530, 1494, 1392, 1350, 1308 cm^{-1}; δ_H: 6.56 (1H, s, NC<u>H</u>ON), 6.83 (2H, m, Ar<u>H</u>), 7.15 (1H, m, Ar<u>H</u>), 7.20 (2H, m, Ar<u>H</u>), 7.45 (3H, m, Ar<u>H</u>), 7.51 (1H, m, Ar<u>H</u>), 7.58 (2H, m, Ar<u>H</u>), 7.90 (1H, m, Ar<u>H</u>), 8.21 (1H, m, Ar<u>H</u>), 8.45 (1H, m, Ar<u>H</u>). δ_C: 101.3 (N<u>C</u>HON), 122.9, 124.8, 125.1, 126.6, 127.4, 128.9, 129.6, 129.8, 130.1 and 133.5 (10 x Ar<u>C</u>H), 127.2 [Ar<u>C</u>(NO_2)], 138.3, 140.4 and 148.2 (3 x *ipso* <u>C</u> of Ar), 153.7 (<u>C</u>$_3$ of oxadiazoline ring). HRMS (ESI^+) exact mass calculated for $C_{20}H_{15}N_3O_3$ [$(M+H)^+$], 346.1192, found 346.1180.

Method 3

A solution of *m*-nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) in distilled dichloromethane (10 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-benzylideneaniline (0.59 g, 3.27 mmol) and triethylamine (0.46 mL, 3.30 mmol) in distilled dichloromethane (15 mL). Following addition, the solution was warmed to room temperature and stirred for 1 h. Water (30 mL) was added and phases separated. The organic phase was washed with water (1 x 20 mL). The organic phase was dried, filtered and the solvent was evaporated *in vacuo* (without heat) to yield *oxadiazoline* (0.54 g, 48%) as brown oil. Recrystallisation from chloroform : hexane was attempted without success. δ_H: 6.56 (1H, s, NC<u>H</u>ON), 6.83 (2H, m, Ar<u>H</u>), 7.16 (1H, m, Ar<u>H</u>), 7.21 (2H, m, Ar<u>H</u>), 7.46 (3H, m, Ar<u>H</u>), 7.52 (1H, m, Ar<u>H</u>), 7.59 (2H, m, Ar<u>H</u>), 7.90 (1H, m, Ar<u>H</u>), 8.23 (1H, m, Ar<u>H</u>), 8.45 (1H, m, Ar<u>H</u>).

Method 4

A solution of *m*-nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) in distilled dichloromethane (10 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-benzylideneaniline (0.59 g, 3.27 mmol) and triethylamine (0.46 mL, 3.30 mmol) in distilled dichloromethane (15 mL). The resulting clear yellow solution was warmed to room temperature and stirred for 6 h. Water (30 mL) was added and the phases were separated. The organic phase was washed with water (1 x 20 mL). The organic phase was dried, filtered and the solvent was evaporated *in vacuo* (without heat) to yield the *oxadiazoline* (0.75 g, 67%) as a brown oil. δ_H: 6.56 (1H, s, NC<u>H</u>ON), 6.83 (2H, m, Ar<u>H</u>), 7.15 (1H, m, Ar<u>H</u>), 7.20 (2H, m, Ar<u>H</u>), 7.45 (3H, m, Ar<u>H</u>), 7.51 (1H, m, Ar<u>H</u>), 7.58 (2H, m, Ar<u>H</u>), 7.90 (1H, m, Ar<u>H</u>), 8.21 (1H, m, Ar<u>H</u>), 8.45 (1H, m, Ar<u>H</u>).

Method 5

A solution of *m*-nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) in ether (10 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylideneaniline (0.59 g, 3.26 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). The mixture was warmed to room temperature and stirred for 10 min. The mixture was filtered and the solvent was removed *in vacuo* to yield the crude *oxadiazoline* (940.00 mg, 84%) as a yellow oil. δ_H: 6.56 (1H, s, NC<u>H</u>ON), 6.83 (2H, m, Ar<u>H</u>), 7.15 (1H, m, Ar<u>H</u>), 7.20 (2H, m, Ar<u>H</u>), 7.45 (3H, m, Ar<u>H</u>), 7.51 (1H, m, Ar<u>H</u>), 7.58 (2H, m, Ar<u>H</u>), 7.90 (1H, m, Ar<u>H</u>), 8.21 (1H, m, Ar<u>H</u>), 8.45 (1H, m, Ar<u>H</u>).

Method 6

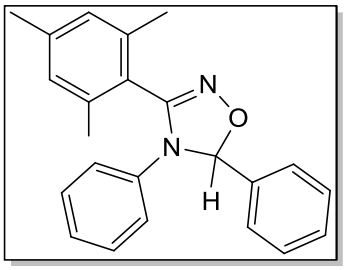
A solution of *m*-nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) in ether (10 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylideneaniline (0.59 g, 3.27 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). The solution was warmed to room temperature and stirred for 1 h. The resulting solution was filtered and the solvent was removed *in vacuo* (without heat) to yield the crude *oxadiazoline* (0.82 g, 73%) as a brown oil. δ_H: 6.56 (1H, s, NC<u>H</u>ON), 6.83 (2H, m, Ar<u>H</u>), 7.15 (1H, m, Ar<u>H</u>), 7.20 (2H, m, Ar<u>H</u>), 7.45 (3H, m, Ar<u>H</u>), 7.51 (1H, m, Ar<u>H</u>), 7.58 (2H, m, Ar<u>H</u>), 7.90 (1H, m, Ar<u>H</u>), 8.21 (1H, m, Ar<u>H</u>), 8.45 (1H, m, Ar<u>H</u>).

Method 7

A solution of *m*-nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) in ether (10 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylideneaniline (0.59 g, 3.26 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). The solution was warmed to room temperature and stirred for 6 h. The resulting solution was filtered and the solvent was removed *in vacuo* (without heat) to yield the crude *oxadiazoline* (0.30 g, 27%) as a brown oil. δ_H: 6.56 (1H, s, NC<u>H</u>ON), 6.83 (2H, m, Ar<u>H</u>), 7.15 (1H, m, Ar<u>H</u>), 7.20 (2H, m, Ar<u>H</u>), 7.45 (3H, m, Ar<u>H</u>), 7.51 (1H, m, Ar<u>H</u>), 7.58 (2H, m, Ar<u>H</u>), 7.90 (1H, m, Ar<u>H</u>), 8.21 (1H, m, Ar<u>H</u>), 8.45 (1H, m, Ar<u>H</u>).

8.3.1.4 3-(2,4,6-Trimethylphenyl)-4-phenyl-5-phenyl-Δ²-1,2,4-oxadiazoline 432

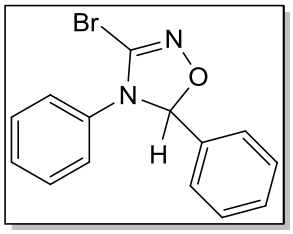
NMR spectroscopy tube reaction



Mesitonitrile-*N*-oxide (12.40 mg, 0.07 mmol) was dissolved in $CDCl_3$ (1.5 mL). This solution was mixed with *N*-benzylideneaniline (13.10 mg, 0.07 mmol) and mixed briskly. A 0.6 mL aliquot of this solution was transferred to an NMR spectroscopy tube and ^1H NMR spectroscopic analysis was carried out immediately, however starting materials (*N*-benzylideneaniline (**346**) and mesitonitrile-*N*-oxide (**7**)) were observed. δ_H: 2.30 (3H, s, ArC<u>H</u>$_3$ **7**), 2.41 [6H, s, Ar(C<u>H</u>$_3$)$_2$ **7**], 6.90 (2H, s, Ar<u>H</u> **7**), 7.23 (3H, m, Ar<u>H</u> **346**), 7.40 (2H, m, Ar<u>H</u> **346**), 7.48 (3H, m, Ar<u>H</u> **346**), 7.91 (2H, m, Ar<u>H</u> **346**), 8.46 (1H, s, N=C<u>H</u> **346**).

8.3.1.5 Attempted preparation of 3-bromo-4-phenyl-5-phenyl-Δ²-1,2,4-oxadiazoline 424

Method 1



Dibromoformaldoxime (1.32 g, 6.49 mmol) in ether (20 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^oC, water/icebath) stirring suspension of *N*-benzylideneaniline (1.18 g, 6.50 mmol) and potassium *tert*-butoxide (0.73 g, 6.51 mmol) in ether (20 mL). On completion of addition, the mixture was warmed to room temperature and was stirred overnight (15 h). The mixture was filtered to remove the precipitate and the solvent was removed *in vacuo.* The resulting sample was placed under high vacuum to remove any residual solvent, yielding a pale orange oil (1.26 g, 64%). A mixture of oxadiazoline (**424**), *N*-benzylideneaniline (**346**) and benzaldehyde (**270**) were observed ina ration of 14 : 69 : 17. ν_{max} (film): 3061, 1697, 1656, 1597, 1558, 1495 cm^{-1}; δ_H: 6.51 (0.2H, s, NC<u>H</u>ON **424**), 6.89 (0.8H, m, Ar<u>H</u> **424**), 7.44 (10.8H, m, Ar<u>H</u> **424**, **346** & **270**), 7.90 (2.5H, m, Ar<u>H</u> **424**, **346** & **270**), 8.47 (1H, s, N=C<u>H</u> **346**), 10.01 (0.25H, s, C<u>H</u>O **270**). m/z = 306 $(M+H)^+$ ^{81}Br **424**, 304 $(M+H)^+$ ^{79}Br **424**, 182 $(M+H)^+$ **346**.

Method 2

Dibromoformaldoxime (2.03 g, 0.01 mol) in ether (30 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^{o}C, water/icebath) stirring solution of *N*-benzylideneaniline (1.81 g, 0.01 mmol) and triethylamine (1.01 g, 0.01 mol) in ether (30 mL). A cloudy, pale orange mixture resulted. On completion of addition, the solution was immediately filtered and the solvent was evaporated *in vacuo* to yield the crude *oxadiazoline* (1.92 g, 63%) as a pale orange oil. The sample was placed under high vacuum to remove any residual solvent. A mixture of oxadiazoline (**424**), *N*-benzylideneaniline (**346**) and benzaldehyde (**270**) were observed in a ratio of 4 : 88 : 8. ν_{max} (film): 3061, 3028, 1701, 1591, 1578, 1486, 1451, 1190 cm^{-1}; δ_H: 6.49 (0.04H, s, NC<u>H</u>ON **424**), 6.91 (0.3H, m, Ar<u>H</u> **424**), 7.24 (3H, m, Ar<u>H</u> **346**), 7.38 (2.2H, m, Ar<u>H</u> **346** & **270**), 7.47 (3.2H, m, Ar<u>H</u> **424**, **346** & **270**), 7.59 (0.2H, m, Ar<u>H</u> **424** & **270**), 7.86 (2.2H, m, Ar<u>H</u> **424**, **346** & **270**), 8.43 (1H, s, N=C<u>H</u> **346**), 9.97 (0.1H, s, C<u>H</u>O **270**). m/z = no assignable peaks.

Method 3

Dibromoformaldoxime (2.03 g, 10.00 mmol) in ether (30 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylideneaniline (1.82 g, 10.03 mmol) and triethylamine (1.01 g, 9.99 mmol) in ether (30 mL). The solution was warmed to room temperature and stirred for 10 min. The precipitate was removed by filtration and solvent evaporated *in vacuo* (without heat) to yield a yellow oil (1.57 g, 52%). A mixture of oxadiazoline (**424**), *N*-benzylideneaniline (**346**) and benzaldehyde (**270**) were observed in a ratio of 3 : 91 : 6. δ_H: 6.50 (0.03H, s, NC<u>H</u>ON **424**), 6.73 (0.05H, m, Ar<u>H</u> **424**), 6.99 (0.06H, m, Ar<u>H</u> **424**), 7.25 (3H, m, Ar<u>H</u> **346** & **424**), 7.39 (2H, m, Ar<u>H</u> **346**), 7.49 (5.2H, m, Ar<u>H</u> **424**, **346** & **270**), 7.89 (2H, m, Ar<u>H</u> **346**), 8.45 (1H, s, C<u>H</u>=N **346**), 10.00 (0.07H, s, C<u>H</u>O **270**).

Method 4

Dibromoformaldoxime (2.03 g, 10.00 mmol) in ether (30 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylideneaniline (1.82 g, 10.03 mmol) and triethylamine (1.01 g, 10.02 mmol) in ether (30 mL). On completion of addition, the solution was warmed to room temperature and stirred for 1 h. The precipitate was removed by filtration and the solvent was evaporated *in vacuo* (without heat) to yield a yellow oil (2.68 g, 89%). A mixture of oxadiazoline (**424**),

N-benzylideneaniline (**346**) and benzaldehyde (**270**) were observed in a ratio of 2 : 93 : 5.δ_H: 6.49 (0.02H, s, NCHON **424**), 6.72 (0.08H, m, ArH **424**), 7.01 (0.06H, m, ArH **424**), 7.19 (3.1H, m, ArH **424**, **346** & **270**), 7.48 (5.3H, m, ArH **424**, **346** & **270**), 7.87 (2.1H, m, ArH **346** & **270**), 8.43 (1H, s, N=CH **346**), 9.98 (0.06H, s, CHO **270**).

Method 5

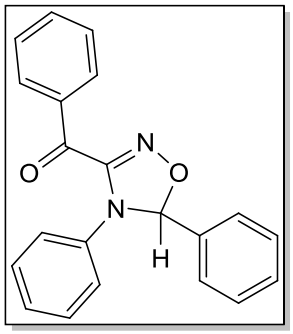
Dibromoformaldoxime (2.0 g, 10.0 mmol) in ether (30 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-benzylidene aniline (1.8 g, 10.0 mmol) and triethylamine (1.0 g, 10.0 mmol) in ether (30 mL). On completion of addition, the solution was warmed to room temperature and stirred for 6 h. The precipitate was removed by filtration and solvent evaporated *in vacuo* (without heat) to yield a mixture of oxadiazoline (**424**), *N*-benzylideneaniline (**346**) and benzaldehyde (**270**) in a ratio of 2 : 84 : 14 as a brown oil.. ν_{max} (film): 3062, 3029, 1701, 1625, 1591, 1578, 1486, 1452, 1190 cm^{-1}; δ_H: 6.51 (0.02H, s, NCHON **424**), 6.75 (0.2H, m, ArH **424**), 7.10 (0.16H, m, ArH **424**), 7.24 (3H, m, ArH **346**), 7.40 (2H, m, ArH **346**), 7.50 (3.2H, m, ArH **424**, **346** & **270**), 7.63 (0.2H, m, ArH **270**), 7.90 (2.3H, m, ArH **346** & **270**), 8.46 (1H, s, N=CH **346**), 10.01 (0.17H, s, CHO **270**).

Method 6

Dibromoformaldoxime (2.03 g, 9.98 mmol) in ether (30 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^oC, water/icebath) stirring solution of *N*-benzylideneaniline (1.82 g, 10.03 mmol) and triethylamine (1.01 g, 10.00 mmol) in ether (30 mL). On completion of addition, the solution was warmed to room temperature and stirred for 19.5 h. The precipitate was removed by filtration and solvent evaporated *in vacuo* (without heat) to yield a mixture of oxadiazoline (**424**), *N*-benzylideneaniline (**346**) and benzaldehyde (**270**) in a ratio of 2 : 75 : 23 as a.dark yellow/light green oil (1.62 g). δ_H: 6.50 (0.03H, s, NCHON **424**), 6.95 (0.34H, m, ArH **424**), 7.22 (3H, m, ArH **346**), 7.38 (2H, m, ArH **346**), 7.48 (3.7H, m, ArH **424**, **346** & **270**), 7.60 (0.4H, m, ArH **270**), 7.87 (2.4H, m, ArH **346** & **270**), 8.44 (1H, s, N=CH **346**), 9.98 (0.3H, s, CHO **270**).

8.3.1.6 3-Benzoyl-4-phenyl-5-phenyl-Δ^2-1,2,4-oxadiazoline 425

Method 1



A solution of 1-benzoyl-1-chloroformaldoxime (1.20 g, 6.53 mmol) in ether (30 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylideneaniline (1.18 g, 6.50 mmol) and triethylamine (0.66 g, 6.50 mmol) in ether (40 mL). The resulting cloudy mixture was stirred for 3 h at room temperature. Water (30 mL) was added to dissolve the precipitate. The resulting biphasic solution was transferred to a separating funnel and phases were separated. The organic phase was washed with water (2 x 30 mL). The combined aqueous layer was then washed with ether (1 x 30 mL). The combined ethereal extracts were dried, filtered and solvent removed *in vacuo*. The resulting residue of the crude oxadiazoline was dried further under high vacuum overnight. Recrystallisation from ethyl acetate: hexane yielded a mixture of the *oxadiazoline* (**425**) and *N*-benzoylaniline (**347**) in a 1 : 1 ratio as a pale orange solid (0.3 g). δ_H: 6.61 (1H, s, NCHON **425**), 6.72 (0.37H, s, ? another form of the oxadiazoline?), 6.81 (1.9H, m, ArH **425**), 6.94 (0.74H, m, ArH ?), 7.13 (4.6H, m, ArH **425** & **347**), 7.47 (11.8H, m, ArH **425** & **347**), 7.66 (3H, m, ArH **425** & **347**), 7.79 (0.7H, bs, NH **347**), 7.87 (1.9H, m, ArH **347**), 8.27 (2H, m, ArH **425**).

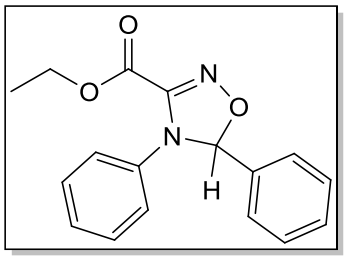
Method 2

A solution of 1-benzoyl-1-chloroformaldoxime (1.19 g, 6.50 mmol) in ether (20 mL) was added dropwise *via* a pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath) stirring solution of *N*-benzylideneaniline (1.18 g, 6.50 mmol) and triethylamine (0.66 g, 6.55 mmol) in ether (20 mL). On completion of addition, the resulting mixture was warmed to room temperature and stirred overnight (15 h). The sample was filtered to remove the precipitate and the solvent was removed *in vacuo* (without heat). The sample was placed under high vacuum to remove any residual solvent (1.57 g, 74%). A mixture of oxadiazoline (**425**), *N*-benzylideneaniline (**346**), *N*-benzoylaniline (**347**) and benzaldehyde (**270**) (38 : 48 : ? : 14).δ_H: 6.61 (1H, s, NCHON **425**), 6.80 (2H, m, ArH **425**), 6.92 (1.1H, m, ArH **425**), 7.17 (9.4H, m, ArH **425**, **346** & **347**), 7.46 (20H, m, ArH **425**, **346**, **347** & **270**), 7.68 (3H, m, ArH **425**, **347** & **270**), 7.89

(5.7H, m, ArH **425**, **346**, **347** & **270**), 8.05 (0.3H, m, ArH **425** ?), 8.19 (1.45H, m, ArH **425**), 8.27 (1.6H, m, ArH **425**), 8.46 (1.28H, s, N=CH **346**), 10.01 (0.36H, s, CHO **270**).

8.3.1.7 3-Ethoxy-4-phenyl-5-phenyl-Δ²-1,2,4-oxadiazoline 426

Method 1



Ethylchloroglyoxalate oxime (0.99 g, 6.51 mmol) in ether (30 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 °C, water/icebath), stirring solution of *N*-benzylideneaniline (1.18 g, 6.50 mmol) and triethylamine (0.66 g, 6.50 mmol) in ether (40 mL). Once addition was complete, the solution was warmed to room temperature and stirred for ten minutes. Water (30 mL) was added to dissolve the precipitate and the resulting biphasic mixture was transferred to a separating funnel and the phases were separated. The organic phase was washed with water (3 x 30 mL). The combined aqueous phases were washed with ether (1 x 30 mL).The combined organic phases were dried, filtered and solvent evaporated *in vacuo* (without heat) and dried under high vacuum to yield the *oxadiazoline* (1.53 g, 79%) as yellow/orange oil. Recrystallisation from ether:hexane (1:5) was attempted. A clear crystalline solid was isolated which contained a mixture of 3,4-diethoxycarbonylfuroxan (**315**), *N*-benzylideneaniline (**346**) and oxadiazoline (**426**) in a ratio of 31 : 63 : 6. δ_H: 1.39 [3H, m, $(CH_3CH_2O)_2$ **315**], 4.45 [2H, two overlapping q, J = 7.15, 7.16, $(CH_3CH_2O)_2$ **315**], 6.50 (0.1H, s, NCHON **426**), 6.72 (0.5H, m, ArH **426**), 6.90 (0.4H, m, ArH **426**), 7.21 (4.05H, m, ArH **426** & **346**), 7.47 (6.15H, m, ArH **426** & **346**), 7.90 (2.3H, m, ArH **426** & **346**), 8.45 (1H, s, N=CH **346**).

Method 2

Ethylchloroglyoxalate oxime (0.99 g, 6.50 mmol) in ether (30 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 °C, water/icebath), stirring solution of *N*-benzylideneaniline (1.18 g, 6.50 mmol) and triethylamine (0.66 g, 6.57 mmol) in ether (40 mL). The resulting cloudy mixture was stirred at room temperature for 3 h. Water (30 mL) was added to the stirring mixture to dissolve the precipitate and the resulting biphasic solution was transferred to a separating funnel and the phases were separated. The organic phase was washed with water (2 x 30 mL) and the combined aqueous phases were washed with ether (1 x 30 mL).The combined organic phases were dried, filtered and solvent evaporated *in vacuo*. The resulting residue of crude oxadiazoline

was dried further under high vacuum overnight. The residue was recrystallised from ethyl acetate : hexane and a mixture of 3,4-diethoxycarbonylfuroxan (**315**), *N*-benzylideneaniline (**346**) and oxadiazoline (**426**) was isolated by vacuum filtration as a dark green solid (20.20 mg). δ_H: 1.38 [3H, m, ($C\underline{H}_3CH_2O)_2$ **315**], 4.44 [2H, two overlapping q, J = 7.15, 7.16, ($CH_3C\underline{H}_2O)_2$ **315**], 6.49 (0.1H, s, NC<u>H</u>ON **426**), 6.79 (0.6H, m, Ar<u>H</u> **426**), 7.22 (3.5H, m, Ar<u>H</u> **426** & **346**), 7.48 (6.2H, m, Ar<u>H</u> **426** & **346**), 7.88 (2.3H, m, Ar<u>H</u> **426** & **346**), 8.44 (1H, s, N=C<u>H</u> **346**).

Method 3

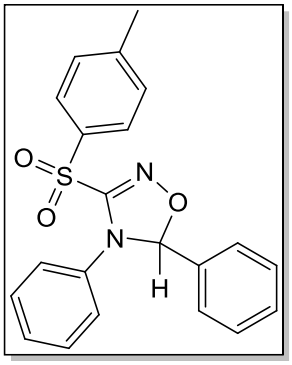
Ethylchloroglyoxalate oxime (0.49 g, 3.26 mmol) in ether (10 mL) was added at a rate of 0.793 mL/min using a syringe pump, to a cooled (<10 ^oC, water/icebath), stirring solution of *N*-benzylideneaniline (0.59 g, 3.25 mmol) and triethylamine (0.33 g, 3.29 mmol) in ether (15 mL). This addition took 12 h 30 min. The solution was maintained at <10 ^oC for the first seven hours and then addition continued at room temperature. The mixture was filtered to remove the precipitate and the solvent was removed *in vacuo* (without heat) to yield the *oxadiazoline* (0.79 g, 82%). The residue was washed with water and recrystallisation from chloroform: hexane was attempted. A dark green solid containing a mixture of 3,4-diethoxycarbonylfuroxan (**315**), *N*-benzylideneaniline (**346**) and oxadiazoline (**426**) was isolated in a ratio of 28 : 63 : 9. δ_H: 1.40 [3H, m, ($C\underline{H}_3CH_2O)_2$ **315**], 4.46 [1.5H, m, ($CH_3C\underline{H}_2O)_2$ **315**], 6.51 (0.3H, s, NC<u>H</u>ON **426**), 6.89 (1.2H, m, Ar<u>H</u> **426** & **346**), 7.25 (4.3H, m, Ar<u>H</u> **426** & **346**), 7.50 (7.3H, m, Ar<u>H</u> **426** & **346**), 7.89 (2.3H, m, Ar<u>H</u> **426** & **346**), 8.46 (1H, s, N=C<u>H</u> **346**).

Method 4

Triethylamine (0.33 g, 3.25 mmol) in ether (10 mL) was added at a rate of 0.793 mL/h *via* syringe pump to a cooled (<10 ^oC, water/icebath), stirring solution of ethylchloroglyoxalate oxime (0.50 g, 3.28 mmol) and *N*-benzylideneaniline (0.59 g, 3.25 mmol) in ether (20 mL). The solution was maintained (<10 ^oC, water/icebath) for 2.5 h, then warmed to room temperature and stirred overnight. The sample was filtered to remove the precipitate. The solvent was evaporated *in vacuo* and any residual solvent was evaporated under high vacuum to yield a mixture of 3,4-diethoxycarbonylfuroxan (**315**), *N*-benzylideneaniline (**346**) and oxadiazoline (**426**) (25 : 50 : 25) as a dark green oil.(0.427 g, 44%) ν_{max} (film): 1742, 1626, 1496, 1194 cm^{-1}; δ_H: 1.38 [3H, m, ($C\underline{H}_3CH_2O)_2$ **315**], 4.44 [1.5H, m, ($CH_3C\underline{H}_3O)_2$ **315**], 6.50 (0.5H, s, NC<u>H</u>ON), 6.82 (1.5H, m, Ar<u>H</u> **426** & **346**),

7.22 (4.7H, m, ArH **426** & **346**), 7.48 (8.5H, m, ArH **426** & **346**), 7.89 (2.3H, m, ArH **426** & **346**), 8.45 (1H, s, N=CH **346**).

8.3.1.8 3-(*p*-Toluenesulfonyl)-4-phenyl-5-phenyl-Δ²-1,2,4-oxadiazoline 427

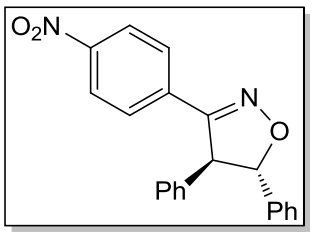


A suspension of 1-*p*-toluenesulfonyl-1-bromoformaldoxime (0.91 g, 3.27 mmol) in ether (10 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylideneaniline (0.59 g, 3.26 mmol) and triethylamine (0.34 g, 3.33 mmol) in ether (15 mL). The solution was warmed to room temperature and stirred overnight (14.5 h). The sample was filtered to remove the precipitate. The solvent was removed *in vacuo* and residual solvent removed under high vacuum to yield *oxadiazoline* (0.87 g, 73%) as a brown oil. Recrystallisation from chloroform:hexane was attempted without success and the crude product mixture was analysed. A mixture of oxadiazoline (**427**), *N*-benzylideneaniline (**346**), *N*-benzoylaniline (**347**), benzaldehyde (**270**) and 3,4-*bis*-(*p*-toluenesulfonyl)-furoxan (**309**) (4 : 29 : ? : 44 : 23) were observed. δ_H: 2.43 (5.7H, m, **309**), 6.56 (0.13H, s, NCHON **427**), 6.94 (3.2H, m, ArH **427** & **347**), 7.31 (13.7H, m, ArH **427**, **346** & **309**), 7.51 (6.2H, m, ArH **427**?, **346**, **347** & **270**), 7.65 (2H, m, ArH **347** & **270**), 7.77 (1.3H, m, ArH **427** & **309**), 7.90 (5.14H, m, ArH **427**, **346**, **347**, **270** & **309**), 8.04 (0.81H, m, ArH **427** & **309**), 8.47 (1H, s, N=CH **346**), 10.03 (1.53H, s, CHO **270**).

8.3.2 1,3-Dipolar cycloaddition reactions with an alkene

8.3.2.1 *Trans*-3-(*p*-nitrophenyl)-4,5-*di*phenyl-1,2-isoxazoline 429

Method 1 NMR spectroscopy tube reaction



Triethylamine (1 mL, 0.07 M solution in $CDCl_3$) was added to a sample vial containing *p*-nitrobenzohydroximoyl chloride (14.60 mg, 0.07 mmol) and a 0.6 mL portion of the resulting yellow solution was submitted for ^{1}H NMR spectroscopic analysis (Exp 10). Once the spectrum was recorded, the contents of the NMR spectroscopy tube were returned to the sample vial. This solution was then transferred to a sample vial containing *trans*-stillbene (12.60 mg, 0.07 mmol) and a 0.6 mL portion of the resulting yellow solution was transferred to an NMR spectroscopy tube and ^{1}H NMR spectroscopic analysis was carried out immediately (Exp 11). ^{1}H NMR

spectroscopic analysis was used to monitor the reaction. *p*-Nitrobenzonitrile-*N*-oxide (**265**) and *trans*-stillbene (**428**) were the products in the initial ^{1}H NMR spectrum. Exp 11 δ_H: 7.11 (2H, bs, HC=CH **428**), 7.26 (2.27H, m, ArH **428**), 7.36 (3.97H, m, ArH **428**), 7.51 (3.86H, m, ArH **428**), 7.70 (1.70H, m, ArH **265**), 8.28 (1.77H, m, ArH **265**).

Exp 12 was submitted for NMR spectroscopic analysis immediately after the ^{1}H NMR spectrum for Exp 11 was recorded. δ_H: 4.71 (0.04H, d, J = 6.08, CH **429**), 5.61 (0.04H, d, J = 6.08, CH **429**), 7.11 (2H, bs, HC=CH **428**), 7.26 (2.36H, m, ArH **428**), 7.36 (4.20H, m, ArH **429** & **428**), 7.52 (3.84H, m, ArH **428**), 7.71 (1.74H, m, ArH **429** & **265**), 8.09 (0.22H, m, ArH **429**), 8.29 (1.87H, m, ArH **265**).

Exp 13 indicates that the 3,4-*bis*-(*p*-nitrophenyl)-furoxan (**312**) began to form: 4.71 (0.30H, d, J = 6.08, CH **429**), 5.61 (0.30H, d, J = 6.08, CH **429**), 7.11 (2H, bs, HC=CH **428**), 7.26 (2.93H, m, ArH **428**), 7.36 (6.37H, m, ArH **429** & **428**), 7.52 (3.85H, m, ArH **428**), 7.72 (1.81H, m, ArH **265** & **429**), 8.05 (0.14H, m, ArH **312**), 8.11 (0.66H, m, ArH **429**), 8.21 (0.28H, m, ArH **312**), 8.29 (1.04H, m, ArH **265** & **312**), 8.38 (0.66H, m, ArH **312**).

Exp 19: 4.71 (0.61H, d, J= 6.08, CH **429**), 5.61 (0.61H, d, J = 6.08, CH **429**), 7.11 (2H, bs, HC=CH **428**), 7.26 (3.91H, m, ArH **428**), 7.37 (8.97H, m, ArH **429** & **428**), 7.74 (1.82H, m, ArH **429**), 7.85 (0.21H, m, ArH **312**), 8.09 (1.52H, m, ArH **429** & **312**), 8.27 (2.41H, m, ArH **429** & **312**).

Method 2

A solution of *p*-nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) in ether (10 mL) was added dropwise *via* pressure-equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *trans*-stillbene (0.59 g, 3.25 mmol) and triethylamine (0.46 mL, 3.30 mmol) in ether (15 mL). The resulting solution was warmed to room temperature and stirred overnight (20 h), filtered and solvent evaporated *in vacuo* (without heat) to yield crude isoxazoline. δ_H: 4.66 (1H, d, J = 6.11, CH **429**), 5.54 (1H, d, J = 6.10, CH **429**), 7.01 (3H, m, ArH), 7.17 (5.28H, m, ArH), 7.29 (14.04H, m, ArH), 7.43 (5.91H, m, ArH), 7.54 (0.72H, m, ArH), 7.64 (2.10H, m, ArH), 7.94 (2.35H, m, ArH), 8.16 (3.03H, m, ArH). m/z = no diagnostic molecular ions. Recrystallisation from chloroform : hexane yielded the *isoxazoline* (0.14 g, 13%) as an orange solid. The recrystallised product was purified by column chromatography [gradient eluent, 10-60% Ethyl acetate : hexane]. F1-6

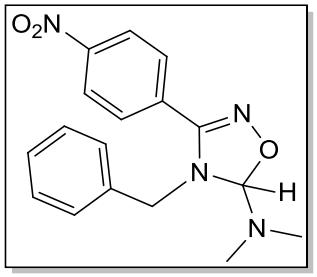
combined and solvent evaporated *in vacuo* to yield a pale yellow solid, 49 mg. δ_H: 4.71 (1H, d, J = 6.09, HC), 5.61 (1H, d, J = 6.17, HC), 7.26 (1.89H, m, ArH), 7.37 (6.41H, m, ArH), 7.75 (1.64H, m, ArH of *p*-NO_2Ar), 8.13 (1.72H, m, ArH of *p*-NO_2Ar), 8.40 (2H, bs, ArH), 8.45 (2H, bs, ArH). F7-10 combined and solvent evaporated *in vacuo* to yield a white solid, 73 mg. Unknown product: δ_H: 7.74 (4H, m, ArH), 8.33 (1H, m, ArH), 8.36 (2H, m, ArH), 8.39 (2.67H, m, ArH), 8.54 (1.75H, bs, ArH). m/z = no diagnostic molecular ions.

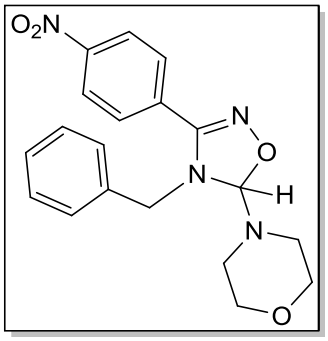
8.4 Competition reactions

To investigate which dipolarophile was more reactive towards the nitrile oxide, the hydroximoyl halide solution was added to a mixture of the two formamidines to be screened. The ratio of oxadiazolines formed was measured using proton NMR spectroscopic analysis

8.4.1 Competition reaction to investigate if *N,N*-dimethyl-*N*-benzylformamidine 339 or *N*-benzylformimidoylmorpholine 318 is more reactive to *p*-nitrobenzonitrile-*N*-oxide 265

p-Nitrobenzohydroximoyl chloride (0.60 g, 3.00 mmol) in dichloromethane (20 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^oC, water/icebath), stirring solution of *N*,*N*-dimethyl-*N*-benzylformamidine (0.24 g, 1.50 mmol) and *N*-benzylformimidoylmorpholine (0.31 g, 1.50 mmol) in dichloromethane (10 mL) and triethylamine (0.30 g, 3.01 mmol) in dichloromethane (10 mL). The resulting yellow mixture was stirred. Water (15 mL) was added to the stirring mixture to dissolve the precipitate. The phases were separated & the organic layer was extracted with water (3 x 15 mL). The aqueous layer was washed with dichloromethane (1 x 15 mL). The organic extracts were combined, filtered, dried and the solvent was evaporated *in vacuo* (without heat). δ_H: 6.07 (1H, s, NCHON **381**), 6.14 (1H, s, NCHON **367**), Ratio (1:1).

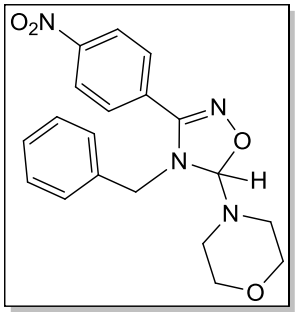




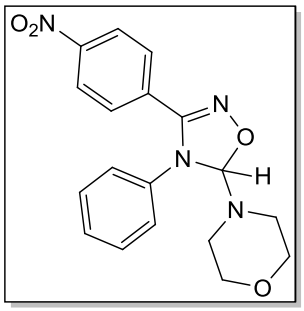
367 **381**

8.4.2 Competition reaction to investigate if *N*-benzylformimidoylmorpholine 318 or *N*-(*N*'-phenylformimidoyl)-morpholine 341 is more reactive to *p*-nitrobenzonitrile-*N*-oxide 265

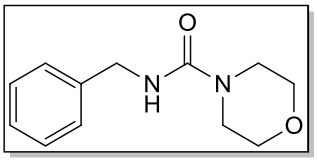
p-Nitrobenzohydroximoyl chloride (0.42 g, 2.11 mmol) in dichloromethane (50 mL) was added dropwise to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N*'-phenylformimidoyl)-morpholine (0.20 g, 1.06 mmol), *N*-benzylformimidoylmorpholine (0.22 g, 1.05 mmol) and triethylamine (0.21 g, 2.11 mmol) in dichoromethane (20 mL). Following the addition, the solution was warmed to room temperature and stirred for 10 min. Water (20 mL) was added to the stirring mixture to dissolve the precipitate and the phases were separated. The organic layer was extracted with water (3 x 20 mL). The organic extracts were combined, dried and the solvent was evaporated on the high vacuum line. (0.47 g) bright yellow solid isolated. δ_H: 1.65 (2.1H, bs, ?), 2.48 (0.39H, bs, ?), 2.79 [2H, m, N(C$\underline{H}_{ax}$)$_2$ **392**], 2.97 [2H, m, N(C$\underline{H}_{eq}$)$_2$ **392**], 3.57 [1.53H, m, N(C$\underline{H}_2$)$_2$ & O(C$\underline{H}_2$)$_2$ **336**], 3.80 [4H, t, J = 4.76, O(C$\underline{H}_2$)$_2$ **392**], 4.43 (0.19H, d, J = 6.46, PhC$\underline{H}_2$ **336**), 4.50 (0.46H, d, J = 5.87, PhC$\underline{H}_2$?), 6.19 (1H, s, NC$\underline{H}$ON **392**), 7.05 (2H, m, Ar$\underline{H}$ **392**), 7.21 (1.04H, m, Ar$\underline{H}$?), 7.26 (4.70H, m, Ar$\underline{H}$ **392** & **336**), 7.69 (2H, m, Ar$\underline{H}$ **392**), 8.18 (2H, m, Ar$\underline{H}$ **392**), 8.34 (1.40H, m, Ar$\underline{H}$?), 8.48 (0.94H, m, Ar$\underline{H}$?), 8.70 (0.48H, m, Ar$\underline{H}$?), 8.90 (0.46H, m, Ar$\underline{H}$?).



381



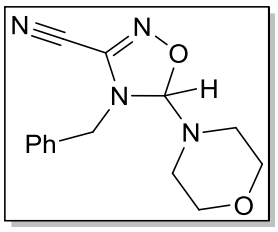
392



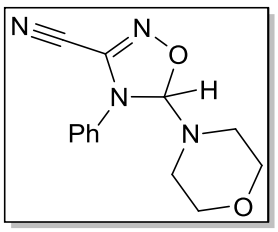
336

8.4.3 Competition reaction to investigate if *N*-benzylformimidoylmorpholine 318 or *N*-(*N*'-phenylformimidoyl)-morpholine 341 is more reactive to cyanoformonitrile-*N*-oxide 435

A solution of cyanoformhydroximoyl chloride (0.21 g, 2.00 mmol) in ether (10 mL) was added dropwise *via* a pressure equalising addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N*'-phenylformimidoyl)-morpholine (0.19 g, 1.00 mmol), *N*-benzylformimidoylmorpholine (0.20 g, 1.00 mmol) and triethylamine (0.28 mL, 2.01 mmol) in ether (20 mL). Following addition, the solution was warmed to room temperature and stirred for 10 min. Water (20mL) was added to dissolve the precipitate. The phrases were separated and the organic phase was dried, filtered and solvent evaporated *in vacuo* (without heat) to yield a yellow oil (0.245 g). Proton NMR spectroscopic analysis showed that oxadiazolines **390** and **402** were obtained in a ratio of 68 : 32 by comparison of the characteristic oxadiazoline CH peak at 6.06 and 6.38 ppm respectively.



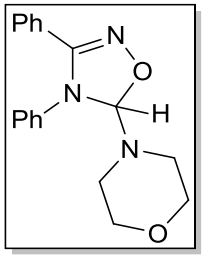
390



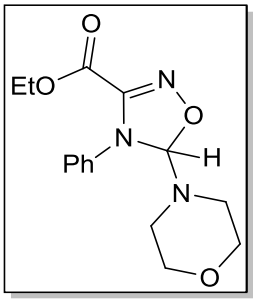
402

8.4.4 Competition reaction to investigate if benzonitrile-*N*-oxide 27 or ethoxycarbonylnitrile-*N*-oxide 376 is more reactive to *N*-(*N*'-phenylformimidoyl)-morpholine 341

Benzohydroximoyl chloride (0.51 g, 3.26 mmol) and ethylchloroglyoxalate oxime (0.49 g, 3.25 mmol) in ether (30 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N*'-phenylformimidoyl)-morpholine (1.23 g, 6.48 mmol) and triethylamine (0.66 g, 6.51 mmol) in ether (40 mL). Following the addition, the solution was warmed to room temperature and the solution was stirred for 10 min. Water (30 mL) was added to dissolve the precipitate and a clear biphasic solution resulted. The solution was transferred to a separating funnel and the phases were separated. The organic layer was extracted with water (3 x 30 mL). The combined aqueous extracts were washed with ether (1 x 30 mL). The organic extracts were combined, dried, filtered and the solvent was evaporated *in vacuo* to yield the crude *oxadiazolines* (1.52 g) as a pale cream solid. Proton NMR spectroscopic analysis shows that oxadiazolines **267** and **400** were observed in a ratio of 59 : 41 by comparison of the characteristic oxadiazoline CH resonances at 6.13 and 6.17 ppm respectively.



267

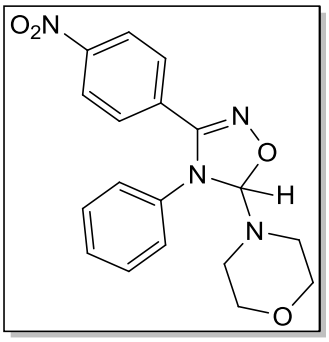


400

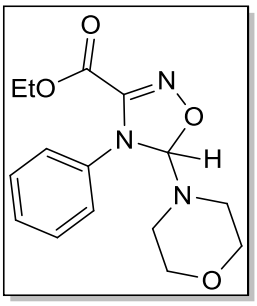
8.4.5 Competition reaction to investigate if *p*-nitrobenzonitrile-*N*-oxide 265 or ethoxycarbonylnitrile-*N*-oxide 376 is more reactive to *N*-(*N*'-phenylformimidoyl)-morpholine 341

p-Nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) and ethylchloroglyoxalate oxime (0.49 g, 3.26 mmol) in ether (30 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N*'-phenylformimidoyl)-morpholine (1.24 g, 6.51 mmol) and triethylamine (0.66 g, 6.51 mmol) in ether (40 mL). Once addition was complete, the ice bath was removed and the solution was stirred for 10 min. Water (30 mL) was added to dissolve the precipitate. The

yellow biphasic solution was then transferred to a separating funnel and the phases were separated. The organic layer was extracted with water (3 x 30 mL). The combined aqueous extracts were washed with ether (1 x 30 mL). The organic extracts were combined, dried, filtered and the solvent was evaporated *in vacuo* (without heat) to yield a yellow oily residue (1.85 g). Proton NMR spectroscopic analysis showed that oxadiazolines **392** and **400** were observed in a ratio of 63 : 37 by comparison of the characteristic oxadiazoline CH resonances at 6.19 and 6.17 ppm respectively.



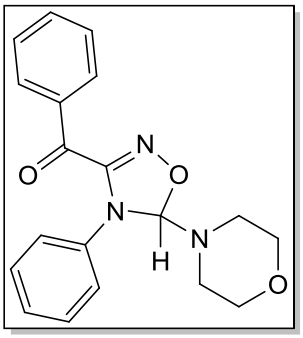
392

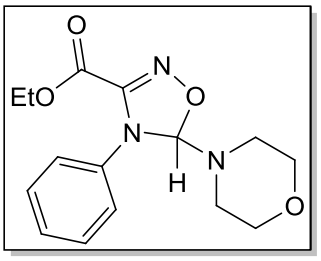


400

8.4.6 Competition reaction to investigate if benzoylnitrile-*N*-oxide 10 or ethoxycarbonylnitrile-*N*-oxide 376 is more reactive to *N*-(*N*'-phenylformimidoyl)-morpholine 341

1-Benzoyl-1-chloroformaldoxime (0.60 g, 3.25 mmol) and ethylchloroglyoxalate oxime (0.49 g, 3.25 mmol) in ether (30 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/ice bath) stirring solution of *N*-(*N*'-phenylformimidoyl)-morpholine (1.24 g, 6.51 mmol) and triethylamine (0.66 g, 6.50 mmol) in ether (40 mL). Once addition was complete, the solution was warmed to room temperature and stirred for 10 min. Water (30 mL) was added to the resulting pale cream solution to dissolve the precipitate and the biphasic solution was transferred to a separating funnel. The phases were separated and the organic phase was extracted with water (3 x 30 mL). The combined aqueous extracts were washed with ether (1 x 30 mL). The organic extracts were combined, dried, filtered and the solvent was evaporated *in vacuo* (without heat) to yield a pale yellow residue (1.66 g). Proton NMR spectroscopic analysis showed that oxadiazolines **400** and **398** were observed in a ratio of 40 : 60 by comparison of the characteristic oxadiazoline CH resonances at 6.17 and 6.25 ppm respectively.

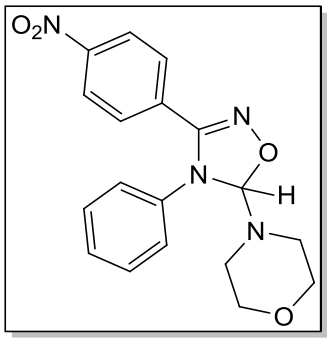


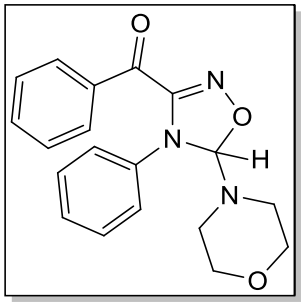


400 **398**

8.4.7 Competition reaction to investigate if benzoylnitrile-*N*-oxide 10 or *p*-nitrobenzonitrile-*N*-oxide 265 is more reactive to *N*-(*N*'-phenylformimidoyl)-morpholine 341

1-Benzoyl-1-chloroformaldoxime (0.60 g, 3.26 mmol) and *p*-nitrobenzohydroximoyl chloride (0.62 g, 3.11 mmol) in ether (30 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-(*N*'-phenylformimidoyl)-morpholine (1.23 g, 6.47 mmol) and triethylamine (0.66 g, 6.50 mmol) in ether (40 mL). Once addition was complete, the solution was warmed to room temperature and stirred for 10 min. Water (30 mL) was added to dissolve the precipitate. The clear yellow biphasic solution was transferred to a separating funnel and the phases were separated. The organic layer was extracted with water (3 x 30 mL). The combined aqueous extracts were washed with ether (1 x 30 mL). The organic extracts were combined, dried, filtered and the solvent was evaporated *in vacuo* (without heat) to yield a yellow solid (0.80 g). Proton NMR spectroscopic analysis showed that oxadiazolines **392** and **398** were observed in a ratio of 46 : 54 by comparison of the characteristic oxadiazoline peaks at 6.18 and 6.25 ppm respectively.

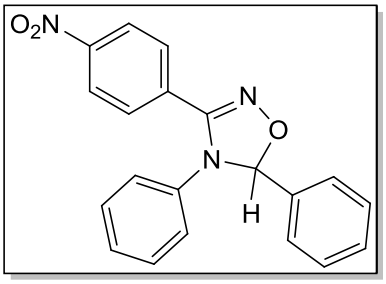




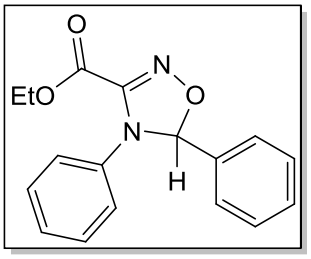
392 **398**

8.4.8 Competition reaction to investigate if *p*-nitrobenzonitrile-*N*-oxide 265 or ethoxycarbonylnitrile-*N*-oxide 376 is more reactive to *N*-benzylideneaniline 346

A solution of *p*-nitrobenzohydroximoyl chloride (0.65 g, 3.25 mmol) and ethylchloroglyoxalate oxime (0.49 g, 3.25 mmol) in ether (30 mL) was added dropwise *via* a pressure equalizing addition funnel to a cooled (<10 ^{o}C, water/icebath), stirring solution of *N*-benzylideneaniline (1.18 g, 6.50 mmol) and triethylamine (0.66 g, 6.50 mmol) in ether (40 mL). Once addition was complete, the solution was warmed to room temperature and stirred for 10 min. Water (30 mL) was added to dissolve the precipitate. The biphasic solution was transferred to a separating funnel and the phases were separated. The organic phase was washed with water (2 x 30 mL). The combined aqueous phases were washed with ether (1 x 30 mL) and dichloromethane (1 x 50 mL, distilled). Phases were separated and combined organic phases were dried, filtered and the solvent was evaporated *in vacuo* to yield a pale yellow solid (1.85 g). Proton NMR spectroscopic analysis showed that oxadiazolines **420** and **426** were observed in a ratio of 8:1 by comparison of the characteristic oxadiazoline peaks at 6.55 and 6.50 ppm respectively.



420



426

9 Appendix 3

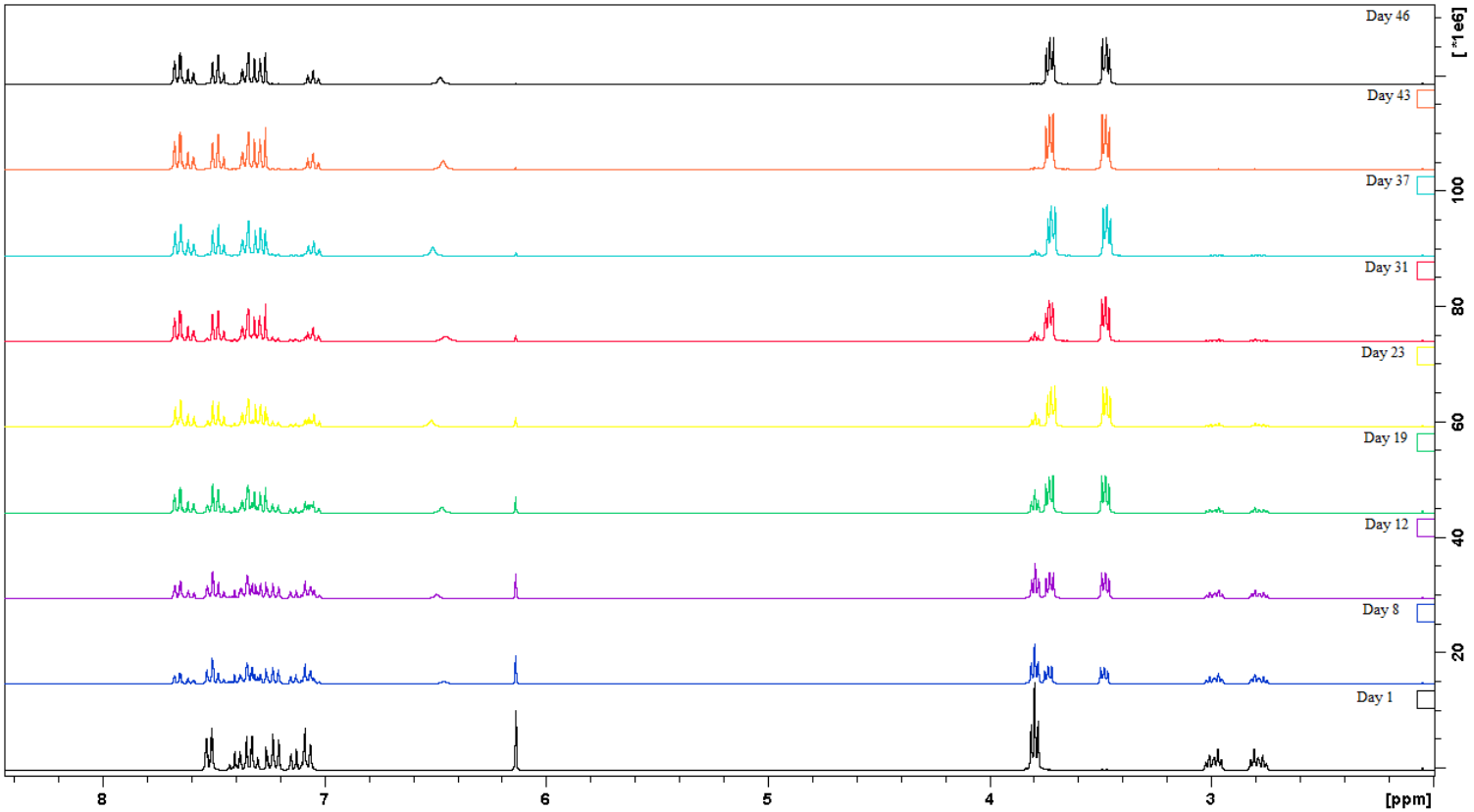


Figure 116 ^{1}H NMR spectra reaction of oxadiazoline 267 ($CDCl_3$, 300MHz) over a 46 d period showing gradual conversion into nitrile 175 and urea 395 as illustrated graphically in Figure 72

Table 44 shows the calculations used to determine the relative rate constant in the formation of oxadiazoline 267 ($CDCl_3$, 300MHz). The conversion of oxadiazoline 267 into urea 395 is illustrated graphically in Figure 72. Figure 74 outlines the determination of relative rate constant, k_{rel}, by plotting $\ln[\text{Oxadiazoline 267}]_{rel}$ *vs* time (d). Figure 75 outlines the determination of relative rate constant, k_{rel}, by plotting $\ln[\text{Urea 395}]_{rel}$ *vs* time (d). Figure 76 portrays the second order rate check by plotting $1/[\text{Oxadiazoline 267}]_{rel}$ *vs* time (d). Figure 77 portrays the second order rate check by plotting $1/[\text{Urea 395}]_{rel}$ *vs* time (d).

Day no	A	B	C	D	E		First order		Second order	
	Oxadiazoline integration (δ_H = 6.13 ppm)	Urea integration (δ_H = 6.42 ppm, relative to oxadiazoline 5-H integration)	Total	$[\text{Oxadiazoline 267}]_{rel}$	$[\text{Urea 395}]_{rel}$	time (sec)	ln $[\text{Ox 267}]_{rel}$	ln $[\text{Urea 395}]_{rel}$	$1/[\text{Oxadiazoline 267}]_{rel}$	$1/[\text{Urea 395}]_{rel}$
			(A+B)	(A/C*100)	(B/C*100)		ln(D)	ln(E)	1/D	1/E
1	1	0	1.00	100.00	0.00	8.64E+04	4.61	-	0.01	-
2	1	0.0594	1.06	94.39	5.61	1.73E+05	4.55	1.72	0.01	0.18
3	1	0.1323	1.13	88.32	11.68	2.59E+05	4.48	2.46	0.01	0.09
4	1	0.2162	1.22	82.22	17.78	3.46E+05	4.41	2.88	0.01	0.06
5	1	0.2886	1.29	77.60	22.40	4.32E+05	4.35	3.11	0.01	0.04
8	1	0.5278	1.53	65.45	34.55	6.91E+05	4.18	3.54	0.02	0.03
9	1	0.6494	1.65	60.63	39.37	7.78E+05	4.10	3.67	0.02	0.03
10	1	0.7506	1.75	57.12	42.88	8.64E+05	4.05	3.76	0.02	0.02
11	1	0.8783	1.88	53.24	46.76	9.50E+05	3.97	3.85	0.02	0.02
12	1	0.9845	1.98	50.39	49.61	1.04E+06	3.92	3.90	0.02	0.02
16	1	1.6728	2.67	37.41	62.59	1.38E+06	3.62	4.14	0.03	0.02
18	1	1.9615	2.96	33.77	66.23	1.56E+06	3.52	4.19	0.03	0.02
19	1	2.207	3.21	31.18	68.82	1.64E+06	3.44	4.23	0.03	0.01
22	1	3.1066	4.11	24.35	75.65	1.90E+06	3.19	4.33	0.04	0.01
23	1	3.3134	4.31	23.18	76.82	1.99E+06	3.14	4.34	0.04	0.01

24	1	3.4189	4.42	22.63	77.37	2.07E+06	3.12	4.35	0.04	0.01
25	1	3.9088	4.91	20.37	79.63	2.16E+06	3.01	4.38	0.05	0.01
26	1	4.4409	5.44	18.38	81.62	2.25E+06	2.91	4.40	0.05	0.01
29	1	5.9718	6.97	14.34	85.66	2.51E+06	2.66	4.45	0.07	0.01
30	1	6.4248	7.42	13.47	86.53	2.59E+06	2.60	4.46	0.07	0.01
31	1	7.1085	8.11	12.33	87.67	2.68E+06	2.51	4.47	0.08	0.01
32	1	7.7623	8.76	11.41	88.59	2.76E+06	2.43	4.48	0.09	0.01
33	1	8.5628	9.56	10.46	89.54	2.85E+06	2.35	4.49	0.10	0.01
36	1	11.6177	12.62	7.93	92.07	3.11E+06	2.07	4.52	0.13	0.01
37	1	13.4117	14.41	6.94	93.06	3.20E+06	1.94	4.53	0.14	0.01
38	1	15.0782	16.08	6.22	93.78	3.28E+06	1.83	4.54	0.16	0.01
40	1	19.2247	20.22	4.94	95.06	3.46E+06	1.60	4.55	0.20	0.01
43	1	31.6809	32.68	3.06	96.94	3.72E+06	1.12	4.57	0.33	0.01
44	1	36.2682	37.27	2.68	97.32	3.80E+06	0.99	4.58	0.37	0.01
46	1	50.0522	51.05	1.96	98.04	3.97E+06	0.67	4.59	0.51	0.01

Table 45 shows the calculations used to determine the relative rate constant in the formation of oxadiazoline 392 ($CDCl_3$, 300MHz). The conversion of oxadiazoline 392 into urea 395 is illustrated graphically in Figure 78. Figure 79 outlines the determination of relative rate constant, k_{rel}, by plotting ln[Oxadiazoline 392]$_{rel}$ *vs* time (d). Figure 80 outlines the determination of relative rate constant, k_{rel}, by plotting ln[Urea 395]$_{rel}$ *vs* time (d). Figure 81 portrays the second order rate check by plotting 1/[Oxadiazoline 392]$_{rel}$ *vs* time (d). Figure 82 portrays the second order rate check by plotting 1/[Urea 395]$_{rel}$ *vs* time (d).

Day no	A	B	C	D	E		First order		Second order	
	Oxadiazoline integration (δ_H = 6.19 ppm)	Urea integration (δ_H = 6.48 ppm, relative to oxadiazoline 5-H integration)	Total	[Oxadiazoline 392]$_{rel}$	[Urea 395]$_{rel}$	time (sec)	ln [Ox 392]$_{rel}$	ln [Urea 395]$_{rel}$	1/[Oxadiazoline 392]$_{rel}$	1/[Urea 395]$_{rel}$
			(A+B)	(A/C*100)	(B/C*100)		ln(D)	ln(E)	1/D	1/E
1	1	0	1.00	100.00	0.00	0.00E+00	4.61	-	0.01	-
2	1	0	1.00	100.00	0.00	1.73E+05	4.61	-	0.01	-
3	1	0	1.00	100.00	0.00	2.59E+05	4.61	-	0.01	-
4	1	0	1.00	100.00	0.00	3.46E+05	4.61	-	0.01	-
5	1	0	1.00	100.00	0.00	4.32E+05	4.61	-	0.01	-
8	1	0.0351	1.04	96.61	3.39	6.91E+05	4.57	1.22	0.01	0.29
9	1	0.0462	1.05	95.58	4.42	7.78E+05	4.56	1.49	0.01	0.23
10	1	0.081	1.08	92.51	7.49	8.64E+05	4.53	2.01	0.01	0.13
11	1	0.1077	1.11	90.28	9.72	9.50E+05	4.50	2.27	0.01	0.10
12	1	0.1296	1.13	88.53	11.47	1.04E+06	4.48	2.44	0.01	0.09
12	1	0.1302	1.13	88.48	11.52	1.04E+06	4.48	2.44	0.01	0.09
15	1	0.2545	1.25	79.71	20.29	1.30E+06	4.38	3.01	0.01	0.05
17	1	0.3151	1.32	76.04	23.96	1.47E+06	4.33	3.18	0.01	0.04
18	1	0.3501	1.35	74.07	25.93	1.56E+06	4.30	3.26	0.01	0.04
21	1	0.4874	1.49	67.23	32.77	1.81E+06	4.21	3.49	0.01	0.03
22	1	0.5089	1.51	66.27	33.73	1.90E+06	4.19	3.52	0.02	0.03
23	1	0.5479	1.55	64.60	35.40	1.99E+06	4.17	3.57	0.02	0.03

24	1	0.6061	1.61	62.26	37.74	2.07E+06	4.13	3.63	0.02	0.03
25	1	0.6565	1.66	60.37	39.63	2.16E+06	4.10	3.68	0.02	0.03
28	1	0.8524	1.85	53.98	46.02	2.42E+06	3.99	3.83	0.02	0.02
29	1	0.9801	1.98	50.50	49.50	2.51E+06	3.92	3.90	0.02	0.02
30	1	0.9954	2.00	50.12	49.88	2.59E+06	3.91	3.91	0.02	0.02
31	1	1.1161	2.12	47.26	52.74	2.68E+06	3.86	3.97	0.02	0.02
32	1	1.1367	2.14	46.80	53.20	2.76E+06	3.85	3.97	0.02	0.02
35	1	1.3684	2.37	42.22	57.78	3.02E+06	3.74	4.06	0.02	0.02
36	1	1.479	2.48	40.34	59.66	3.11E+06	3.70	4.09	0.02	0.02
37	1	1.5761	2.58	38.82	61.18	3.20E+06	3.66	4.11	0.03	0.02
39	1	1.8131	2.81	35.55	64.45	3.37E+06	3.57	4.17	0.03	0.02
42	1	2.1607	3.16	31.64	68.36	3.63E+06	3.45	4.22	0.03	0.01
43	1	2.2704	3.27	30.58	69.42	3.72E+06	3.42	4.24	0.03	0.01
45	1	2.5343	3.53	28.29	71.71	3.89E+06	3.34	4.27	0.04	0.01
49	1	3.2091	4.21	23.76	76.24	4.23E+06	3.17	4.33	0.04	0.01
50	1	3.3501	4.35	22.99	77.01	4.32E+06	3.13	4.34	0.04	0.01
59	1	5.1871	6.19	16.16	83.84	5.10E+06	2.78	4.43	0.06	0.01
63	1	6.67769	7.68	13.02	86.98	5.44E+06	2.57	4.47	0.08	0.01
64	1	6.9572	7.96	12.57	87.43	5.53E+06	2.53	4.47	0.08	0.01
67	1	8.1285	9.13	10.95	89.05	5.79E+06	2.39	4.49	0.09	0.01
72	1	10.6569	11.66	8.58	91.42	6.22E+06	2.15	4.52	0.12	0.01
79	1	13.88622	14.89	6.72	93.28	6.83E+06	1.90	4.54	0.15	0.01
81	1	15.0643	16.06	6.22	93.78	7.00E+06	1.83	4.54	0.16	0.01

Table 46 shows the calculations used to determine the relative rate constant in the formation of oxadiazoline 398 ($CDCl_3$, 300MHz). The conversion of oxadiazoline 398 into urea 395 is illustrated graphically in Figure 86. Figure 87 outlines the determination of relative rate constant, k_{rel}, by plotting ln[Oxadiazoline 398]$_{rel}$ *vs* time (d). Figure 88 outlines the determination of relative rate constant, k_{rel}, by plotting ln[Urea 395]$_{rel}$ *vs* time (d). Figure 89 portrays the second order rate check by plotting 1/[Oxadiazoline 398]$_{rel}$ *vs* time (d). Figure 90 portrays the second order rate check by plotting 1/[Urea 395]$_{rel}$ *vs* time (d).

Day no	A	B	C	D	E		First order		Second order	
	Oxadiazoline integration (δ_H = 6.26 ppm)	Urea integration (δ_H = 6.48 ppm, relative to oxadiazoline 5-H integration)	Total	[Oxadiazoline 398]$_{rel}$	[Urea 395]$_{rel}$	time (sec)	ln [Ox 398]$_{rel}$	ln [Urea 395]$_{rel}$	1/[Oxadiazoline 398]$_{rel}$	1/[Urea 395]$_{rel}$
			(A+B)	(A/C*100)	(B/C*100)		ln(D)	ln(E)	1/D	1/E
0	1	0	1.00	100.00	0.00	0.00E+00	4.61	#NUM!	0.01	#DIV/0!
1	1	0.0042	1.00	99.58	0.42	8.64E+04	4.60	-0.87	0.01	2.39
2	1	0.0045	1.00	99.55	0.45	1.73E+05	4.60	-0.80	0.01	2.23
3	1	0.0047	1.00	99.53	0.47	2.59E+05	4.60	-0.76	0.01	2.14
4	1	0.0047	1.00	99.53	0.47	3.46E+05	4.60	-0.76	0.01	2.14
5	1	0.0048	1.00	99.52	0.48	4.32E+05	4.60	-0.74	0.01	2.09
8	1	0.0048	1.00	99.52	0.48	6.91E+05	4.60	-0.74	0.01	2.09
9	1	0.0049	1.00	99.51	0.49	7.78E+05	4.60	-0.72	0.01	2.05
10	1	0.007	1.01	99.30	0.70	8.64E+05	4.60	-0.36	0.01	1.44
11	1	0.008	1.01	99.21	0.79	9.50E+05	4.60	-0.23	0.01	1.26
12	1	0.0085	1.01	99.16	0.84	1.04E+06	4.60	-0.17	0.01	1.19
16	1	0.01	1.01	99.01	0.99	1.38E+06	4.60	-0.01	0.01	1.01
18	1	0.01	1.01	99.01	0.99	1.56E+06	4.60	-0.01	0.01	1.01
19	1	0.0102	1.01	98.99	1.01	1.64E+06	4.60	0.01	0.01	0.99
23	1	0.0115	1.01	98.86	1.14	1.99E+06	4.59	0.13	0.01	0.88
24	1	0.0128	1.01	98.74	1.26	2.07E+06	4.59	0.23	0.01	0.79
25	1	0.0144	1.01	98.58	1.42	2.16E+06	4.59	0.35	0.01	0.70

26	1	0.0148	1.01	98.54	1.46	2.25E+06	4.59	0.38	0.01	0.69
29	1	0.0156	1.02	98.46	1.54	2.51E+06	4.59	0.43	0.01	0.65
30	1	0.0178	1.02	98.25	1.75	2.59E+06	4.59	0.56	0.01	0.57
31	1	0.0171	1.02	98.32	1.68	2.68E+06	4.59	0.52	0.01	0.59
32	1	0.0196	1.02	98.08	1.92	2.76E+06	4.59	0.65	0.01	0.52
33	1	0.0197	1.02	98.07	1.93	2.85E+06	4.59	0.66	0.01	0.52
36	1	0.0227	1.02	97.78	2.22	3.11E+06	4.58	0.80	0.01	0.45
37	1	0.0232	1.02	97.73	2.27	3.20E+06	4.58	0.82	0.01	0.44
38	1	0.0239	1.02	97.67	2.33	3.28E+06	4.58	0.85	0.01	0.43
40	1	0.0249	1.02	97.57	2.43	3.46E+06	4.58	0.89	0.01	0.41
43	1	0.0276	1.03	97.31	2.69	3.72E+06	4.58	0.99	0.01	0.37
44	1	0.0293	1.03	97.15	2.85	3.80E+06	4.58	1.05	0.01	0.35
46	1	0.032	1.03	96.90	3.10	3.97E+06	4.57	1.13	0.01	0.32
50	1	0.0365	1.04	96.48	3.52	4.32E+06	4.57	1.26	0.01	0.28
51	1	0.0399	1.04	96.16	3.84	4.41E+06	4.57	1.34	0.01	0.26
60	1	0.0532	1.05	94.95	5.05	5.18E+06	4.55	1.62	0.01	0.20
64	1	0.0596	1.06	94.38	5.62	5.53E+06	4.55	1.73	0.01	0.18
65	1	0.0611	1.06	94.24	5.76	5.62E+06	4.55	1.75	0.01	0.17
68	1	0.0661	1.07	93.80	6.20	5.88E+06	4.54	1.82	0.01	0.16
73	1	0.075	1.08	93.02	6.98	6.31E+06	4.53	1.94	0.01	0.14
80	1	0.0882	1.09	91.89	8.11	6.91E+06	4.52	2.09	0.01	0.12
82	1	0.0953	1.10	91.30	8.70	7.08E+06	4.51	2.16	0.01	0.11
85	1	0.0966	1.10	91.19	8.81	7.34E+06	4.51	2.18	0.01	0.11
87	1	0.0995	1.10	90.95	9.05	7.52E+06	4.51	2.20	0.01	0.11
99	1	0.1286	1.13	88.61	11.39	8.55E+06	4.48	2.43	0.01	0.09
108	1	0.1413	1.14	87.62	12.38	9.33E+06	4.47	2.52	0.01	0.08

124	1	0.1824	1.18	84.57	15.43	1.07E+07	4.44	2.74	0.01	0.06
136	1	1.2095	2.21	45.26	54.74	1.18E+07	3.81	4.00	0.02	0.02

Table 47 shows the calculations used to determine the relative rate constant in the formation of oxadiazoline 400 ($CDCl_3$, 300MHz). The conversion of oxadiazoline 400 into urea 395 is illustrated graphically in Figure 92. Figure 93 outlines the determination of relative rate constant, k_{rel}, by plotting $\ln[\text{Oxadiazoline 400}]_{rel}$ *vs* time (d). Figure 94 outlines the determination of relative rate constant, k_{rel}, by plotting $\ln[\text{Urea 395}]_{rel}$ *vs* time (d). Figure 95 portrays the second order rate check by plotting $1/[\text{Oxadiazoline 400}]_{rel}$ *vs* time (d). Figure 96 portrays the second order rate check by plotting 1/[Urea 395] *vs* time (d).

Day no	A	B	C	D	E		First order		Second order	
	Oxadiazoline integration (δ_H = 6.17 ppm)	Urea integration (δ_H = 6.48 ppm, relative to oxadiazoline 5-H integration)	Total	$[\text{Oxadiazoline 400}]_{rel}$	$[\text{Urea 395}]_{rel}$	time (sec)	$\ln[\text{Ox 400}]_{rel}$	$\ln[\text{Urea 395}]_{rel}$	$1/[\text{Oxadiazoline 400}]_{rel}$	$1/[\text{Urea 395}]_{rel}$
			(A+B)	(A/C*100)	(B/C*100)		ln(D)	ln(E)	1/D	1/E
0.0000	1	0	1.00	100.00	0	0.00E+00	4.61	#NUM!	0.01	#DIV/0!
0.6240	1	0	1.00	100.00	0	5.39E+04	4.61	#NUM!	0.01	#DIV/0!
0.9965	1	0.09	1.09	91.74	8.257	8.61E+04	4.52	2.11	0.01	0.12
4.2979	1	0.31	1.31	76.34	23.66	3.71E+05	4.34	3.16	0.01	0.04
5.0417	1	0.35	1.35	74.07	25.93	4.36E+05	4.31	3.26	0.01	0.04
6.0132	1	0.38	1.38	72.46	27.54	5.20E+05	4.28	3.32	0.01	0.04
7.0430	1	0.44	1.44	69.44	30.56	6.09E+05	4.24	3.42	0.01	0.03
8.0229	1	0.55	1.55	64.52	35.48	6.93E+05	4.17	3.57	0.02	0.03
11.1063	1	0.86	1.86	53.76	46.24	9.60E+05	3.98	3.83	0.02	0.02
11.5882	1	0.96	1.96	51.02	48.98	1.00E+06	3.93	3.89	0.02	0.02
12.6660	1	1.14	2.14	46.73	53.27	1.09E+06	3.84	3.98	0.02	0.02
13.6625	1	1.23	2.23	44.84	55.16	1.18E+06	3.80	4.01	0.02	0.02
14.6660	1	1.43	2.43	41.15	58.85	1.27E+06	3.72	4.07	0.02	0.02
17.6389	1	1.78	2.78	35.97	64.03	1.52E+06	3.58	4.16	0.03	0.02
18.7556	1	2.15	3.15	31.75	68.25	1.62E+06	3.46	4.22	0.03	0.01
19.6625	1	2.4	3.40	29.41	70.59	1.70E+06	3.38	4.26	0.03	0.01
21.6174	1	2.75	3.75	26.67	73.33	1.87E+06	3.28	4.30	0.04	0.01
24.8354	1	3.61	4.61	21.69	78.31	2.15E+06	3.08	4.36	0.05	0.01
25.6868	1	4.38	5.38	18.59	81.41	2.22E+06	2.92	4.40	0.05	0.01
27.6514	1	4.81	5.81	17.21	82.79	2.39E+06	2.85	4.42	0.06	0.01
31.8840	1	7.7	8.70	11.49	88.51	2.75E+06	2.44	4.48	0.09	0.01
32.7833	1	8.82	9.82	10.18	89.82	2.83E+06	2.32	4.50	0.10	0.01

41.8465	1	17.72	18.72	5.34	94.66	3.62E+06	1.68	4.55	0.19	0.01

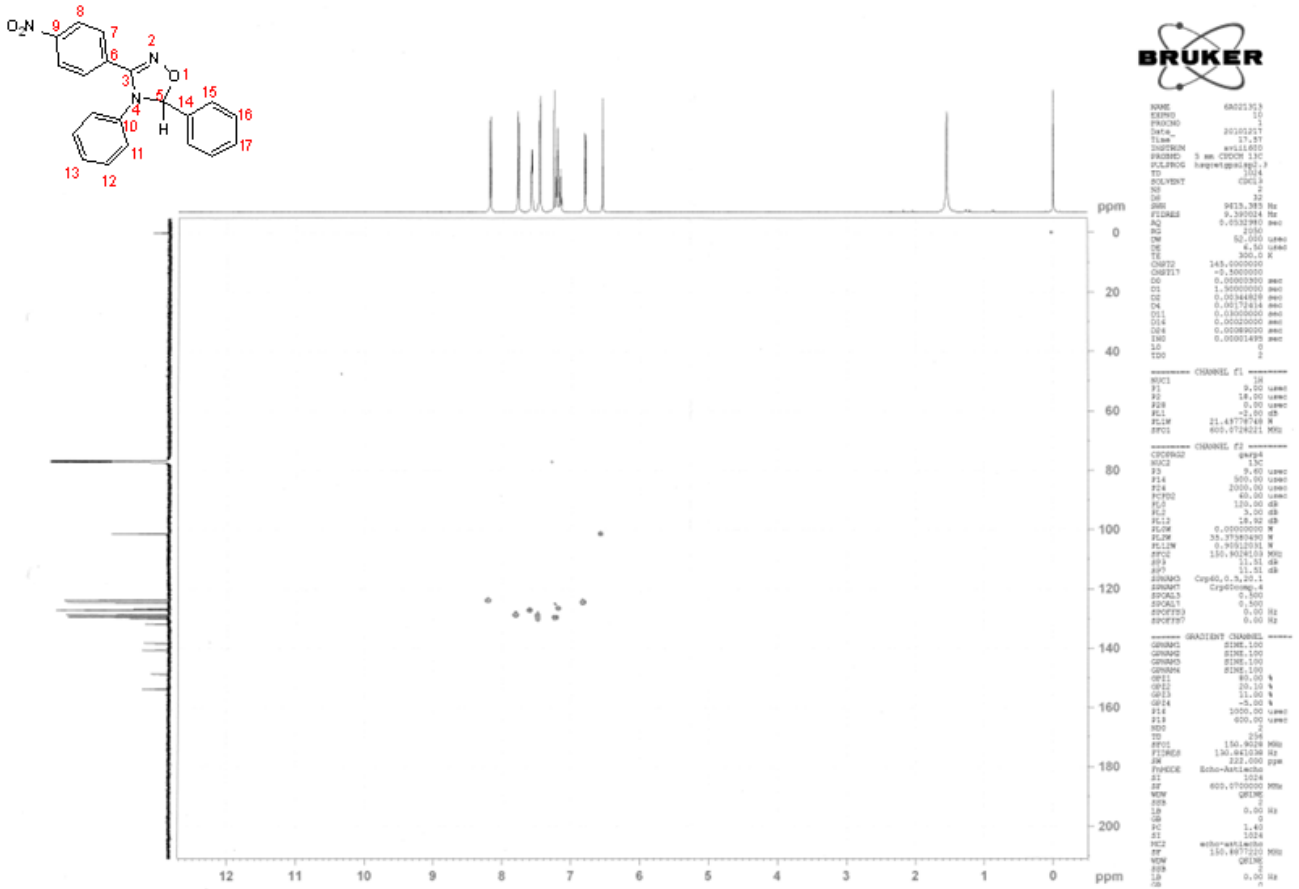


Figure 117 HSQC spectrum of oxadiazoline 420 ($CDCl_3$, 600MHz)

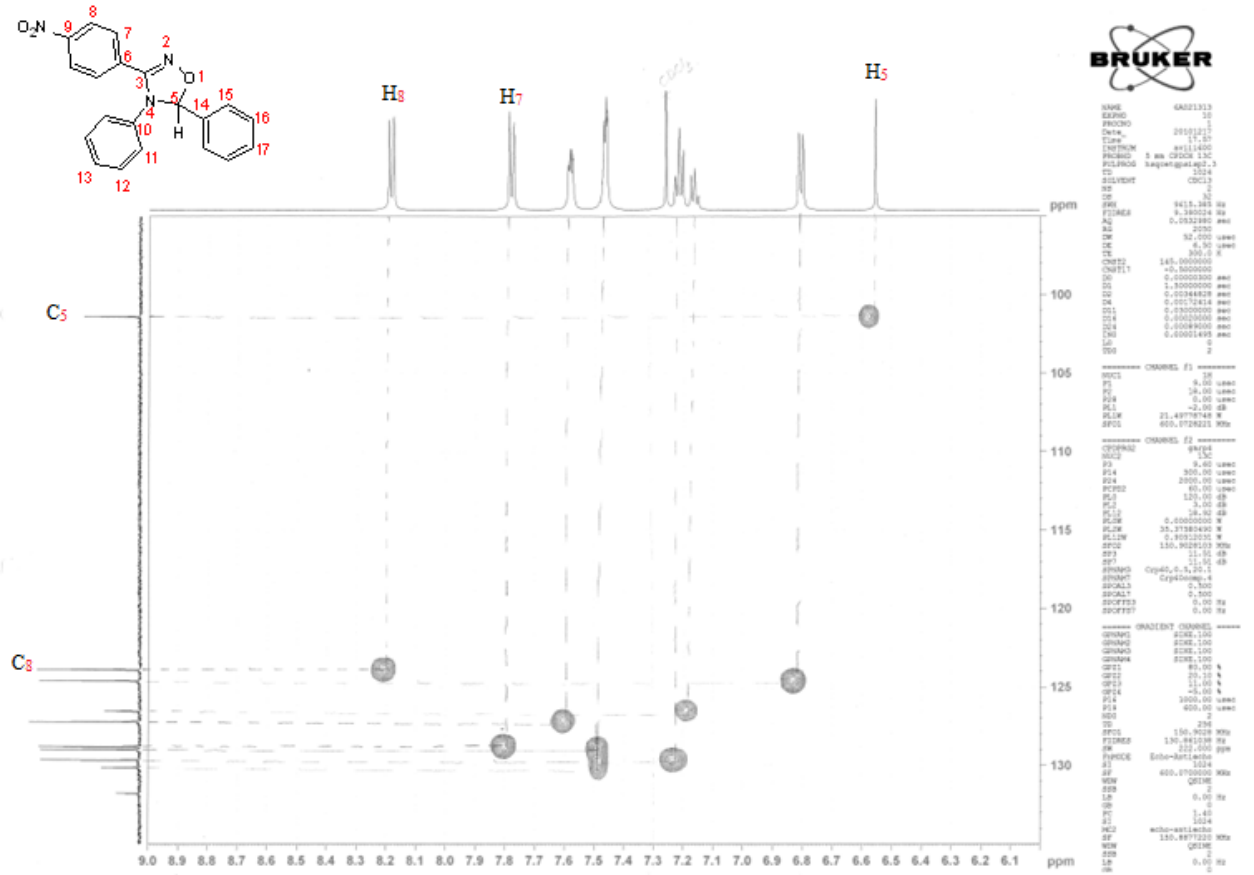


Figure 118 Expanded HSQC spectrum of oxadiazoline 420 ($CDCl_3$, 600MHz)

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